The auditory cortex: perception, memory, plasticity and the influence of musicianship

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by
Nadine Gaab
of Germany

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Professor Lutz Jäncke, Ph.D.
Professor Ulrike Ehlert, Ph.D.

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“ You don’t need any brains to listen to music”
- Luciano Pavarotti-

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Summary

Based on a review of the literature regarding the physiological basis of hearing and auditory processing, brain plasticity and the principles of functional magnet resonance imaging, six studies (A-F) were designed. The general aims of these studies were the assessment of perception, plasticity and memory in the auditory system as well as the influence of performance, gender, musicianship and sleep on auditory processing and learning. Each study employed the same pitch memory task, which was designed based on several criteria outlined in chapter 5 and tested in a pilot study.

To date, human functional imaging studies assessing pitch processing or auditory short-term memory have not revealed a consistent activation pattern. It remains unclear whether only primary and/or secondary auditory brain regions play a role in short-term pitch memory or whether other extratemporal regions are also involved. Furthermore, it is unsolved whether those network components are involved simultaneously or successively.

Study A was designed for the purpose of investigating and evaluating the functional anatomy of a pitch memory task specifically developed for these experiments. Eighteen subjects listened to the pitch memory task, which consisted of a sequence of tones for a duration of 4.6 seconds, and then had to use a button press response to indicate whether or not the last or second to last tone (depending on a visual prompt) was the same or different than the first tone. This task was contrasted with a motor control condition in which subjects pressed a right or left button depending on a visual prompt. To avoid interference with the noise created by the switching of the gradient coils each time the MR signal is read out, a sparse temporal sampling fMRI method with a long repetition time (TR=17s) was used. As a result, the clustered volume MR acquisition and the actual auditory stimulation became completely separated. Additionally, the stimulus-to-imaging delay varied over 7 seconds in a jitter-like fashion in order to explore the time course of brain activation in response to the perceptual and cognitive demands of the pitch memory task. The analysis showed a dynamic activation pattern involving the superior temporal gyrus (STG), supramarginal gyrus (SMG), posterior dorsolateral frontal regions, and superior parietal regions. Bilateral dorsolateral cerebellar regions and the left inferior frontal gyrus were also activated. By regressing the performance score in the pitch memory task with task-related MR signal changes, the SMG and the dorsolateral

cerebellum were significantly correlated with good task performance. The SMG and the dorsolateral cerebellum may play a critical role in short-term storage of pitch information and the continuous pitch discrimination necessary for performing this pitch memory task.

In **study B**, the same experimental and scanning paradigm as in study A was employed to investigate the effects of training on the neural correlates of pitch memory. The neural effect of auditory learning studies in humans have not been studied and described as thoroughly as the neural effects of learning in other domains. Furthermore, it is uncertain whether auditory learning effects can be seen only in traditional auditory regions or whether they may be seen in polymodal association regions. It has also not yet been determined whether signal changes are related to performance improvement over the time course of auditory learning.

The learning group (n=14) underwent daily training sessions in pitch memory (1 hr per day for 5 days) in between two fMRI scans (separated by a week). The control group (n=10) had no training. Based on a Cluster Analysis of the improvement scores, the training group was divided into a "strong" learner and a "weak" learner group. When the activation patterns of the pre- and post-training session were contrasted, the strong learner group showed a positive signal change in auditory regions on the left while a bilateral negative change was apparent in the superior parietal cortex. Following the training period, the weak learner group activated the lingual, inferior frontal, and parahippocampal gyrus while a negative change was seen in the anterior cingulate gyrus. When the post versus pre training images were compared between the two sub-groups, the SMG was significantly more activated in the strong learner group compared to the weak learner group. Thus, the SMG is of critical importance in performing well in this learning experiment, which is further supported by finding a covariation between SMG signal changes and performance score in the previous experiment.

Numerous studies have shown pronounced functional differences in perysylvian regions between musicians and non-musicians for various tasks. Typically, increased musical sophistication was associated with more left-lateralized activation. However, it is unclear whether the between-group differences are a result of differences in performance of experimental tasks, in cognitive strategies, or even differences in anatomical structures.

Study C investigated pitch memory processing differences between musicians and non-musicians. Both groups showed bilateral activation of the STG, SMG, posterior middle, inferior frontal gyrus, and superior parietal lobe, but there was a clear left-sided dominance in both groups. Compared to non-musicians, musicians exhibited greater right temporal and SMG activation (right more than left), though non-musicians showed more right primary and left secondary auditory cortex activation. Given that both groups' exhibited equivalent performance scores, these results most likely denote processing differences between groups, which are potentially related to musical training. Whereas musicians prefer to use brain regions specialized in short-term memory and recall to perform well in this pitch memory task, non-musicians relied more on brain regions necessary for pitch discrimination. Nevertheless, it still unclear whether these differences between musicians and non-musicians are due to variations in brain structure or intensive musical training.

Study D, which was designed to address this issue, matched the performance scores and gender of the strong learner group (n=7) of study B to a group of fourteen musicians who underwent the same fMRI-experiment. When the musician and non-musician groups were compared prior to training the non-musicians, the non-musician group showed more left-sided primary auditory cortex activation. Musicians, on the other hand, activated more the SMG (i.e. short term auditory storage region) on the left. A comparison of the two groups following the training session indicated that the activation pattern in the non-musician group was similar to that of the musician group; nevertheless, the non-musician group exhibited even stronger left-sided temporal lobe activation than the musician group. While a performance difference between non-musicians and musicians was present prior to the training of the non-musicians, there was no significant difference anymore after training. The shift in activation pattern to a left-ward dominance after training and a similar activation of the SMG by the trained non-musicians after training lends support to the notion that functional differences between musicians and non-musicians can be at least partially explained by training that musicians go through.

Several studies have demonstrated the effect of gender on brain structure and function. Functional studies have corroborated this difference by showing gender differences in language processing with females showing a less lateralized activation pattern than males.

Study E investigated possible differences in hemispheric processing between males and females in music related functions using the pitch memory task. In both anterior and posterior perisylvian regions, gender differences were found over the time course of activation. Specifically, male subjects had greater left lateralized activations in anterior and posterior perisylvian regions as well as cerebellar activation bilaterally, while females showed more prominently posterior cingulate/retrosplenial cortex activation compared to males. Although activation patterns differed, there was no difference in the behavioral performance between the two genders. These data indicate that similar to language studies males rely more on left lateralized hemispheric processing even for a musical task.

Several recent studies have demonstrated the importance of sleep in visual and motor skill learning, but the influence of sleep on auditory learning has not yet been explored.

Study F was designed to examine the influence of sleep on the behavioral correlate of auditory learning. Fifty-six subjects were randomly assigned to two groups, trained and behaviorally tested on a pitch-memory task three times during a 24hr period. The morning group began at 9am, was re-tested at 9pm, and again at 9am after a period of sleep. The evening group began at 9pm, was retested at 9am (after sleep) and again at 9pm after a period with no sleep. Regardless of order, both groups showed a significant improvement in performance only after sleep but not after periods of wakefulness, which indicates that sleep plays a critical role in the consolidation of auditory-skill memory tasks.

Overall, the research described in these studies reveals important findings regarding the time course and functional anatomy of pitch perception and pitch memory, training–induced functional changes following a short-term training period, and the influence of musicianship, gender and sleep on pitch memory processing and auditory learning. The most important findings with regard to the neural correlates of pitch memory were the roles of the SMG and the cerebellum in this pitch task. Both brain regions were not previously implicated as having a role in pitch processing and memory.

The studies described above further demonstrate the need to include performance scores in analyses of functional imaging data. Furthermore, the presented data was integrated into a theoretical framework proposed by Petersen et al. (1998), which seeks to explain effects of practice on the functional anatomy of a given task.

Nevertheless, additional theoretical and empirical research is necessary in order to investigate the relationship between cortical plasticity and auditory learning in greater detail.

Zusammenfassung

Basierend auf einem Literaturüberblick über die physiologische Basis des Hörens und der auditorischen Informationsverarbeitung, sowie über Plastizität im Gehirn und den Prinzipien der funktionellen Magnetresonanztomographie wurden in dieser Arbeit sechs Studien (A-F) entwickelt und durchgeführt. Ziel der vorliegenden Arbeit lag in der detaillierten Untersuchung von Wahrnehmung, Plastizität und Gedächtnis im auditorischen Bereich des Gehirns. Darüber hinaus sollte der Einfluss von Performanz, Geschlecht, musikalischer Erfahrung und Schlaf auf die auditorische Informationsverarbeitung und das auditorische Lernen näher untersucht werden.

Basierend auf speziellen Kriterien, die in Kapitel 5 näher erläutert werden, wurde ein experimentelles Paradigma zur Untersuchung des Tonhöhengedächtnisses entwickelt und mit Hilfe einer Pilotstudie überprüft.

Bisher konnte für den Humanbereich noch kein eindeutiges funktionelles Aktivierungsmuster für Tonhöhenverarbeitung sowie auditorisches Kurzzeit- oder Arbeitsgedächtnis nachgewiesen werden. Es bleibt unklar, ob nur primär und/oder sekundär auditorische Areale oder auch andere, nicht auditorische Areale beim Tonhöhenkurzzeitgedächtnis eine Rolle spielen. Darüber hinaus stellt sich die Frage, ob diese Netzwerkkomponenten gleichzeitig oder sukzessive beteiligt sind.

Ziel der **Studie A** war die Untersuchung und Evaluation der funktionellen Anatomie des entwickelten Tonhöhengedächtnisparadigmas mit Hilfe der funktionellen Kernspintomographie (fMRT). Achtzehn Probanden wurden mit diesem Paradigma im Kernspintomographen untersucht. Die Probanden hörten eine Tonsequenz von 4.6 Sekunden Dauer und mussten nach einem visuellen Wortsignal mit Knopfdruck entscheiden, ob der erste und der letzte bzw. vorletzte Ton identisch oder verschieden war. Dieses Paradigma wurde mit einer motorischen Kontrollaufgabe kontrastiert, bei der die Probanden nach einem visuellen Wortsignal den rechten oder linken Knopf drücken mussten. Um Interferenzen mit dem Hintergrundgeräusch des Kernspintomographens zu vermeiden, welches durch den Wechsel der Gradienten entsteht, wurde eine sogenannte “sparse temporal sampling” Methode mit einer langen Repetitionszeit von17 Sekunden verwendet. Das Resultat ist eine vollständige Trennung der Volumenaufnahme und der auditorischen Stimulation. Zusätzlich wurde der Abstand zwischen der Stimulation und der Bildakquisition über sieben Sekunden

variiert, um den Zeitverlauf der durch die perzeptuellen und kognitiven Anforderungen induzierten Hirnaktivierung abzubilden.

Die Analyse zeigte ein dynamisches Aktivierungsmuster über die Zeit, mit Aktivierungen im Gyrus temporalis superior (STG), im Gyrus supramarginalis (SMG), im posterioren Teil der dorsolateralen Frontalregionen und posterioren Teilen des Lobulus parietalis. Zusätzlich waren bilaterale Regionen des dorsolateralen Zerebellums und der linke Gyrus frontalis inferior aktiviert. Eine Regression der funktionellen Aktivierungen mit den Verhaltensdaten der Tonhöhengedächtnis-aufgabe zeigte eine signifikante Korrelation zwischen dem SMG, dem dorsolateralen Zerebellum und guter Performanz in der Tonhöhengedächtnisaufgabe. Der SMG und der dorsolaterale Teil des Zerebellums scheinen eine entscheidende Rolle sowohl bei der Kurzzeitspeicherung von Tonhöheninformation, als auch bei der kontinuierlichen Tonhöhendiskrimination zu spielen, jenen zwei Komponenten, die entscheidend zur erfolgreichen Aufgabenperformanz beizutragen scheinen.

Studie B verwendet das gleiche experimentelle fMRT-Design wie schon in Studie A, um den Einfluss eines Trainings auf die neuronalen Korrelate der entwickelten Tonhöhengedächtnisaufgabe nachzuweisen. Der Einfluss eines auditorischen Trainings auf neuronale Korrelate wurde bisher kaum untersucht. Darüber hinaus bleibt unklar, ob sich auditorische Lerneffekte in traditionellen auditorischen Arealen oder mehr in polymodalen Assoziationsregionen wiederspiegeln, und ob über den gesamten Zeitverlauf des Lernens gesehen, diese Signalveränderungen in Zusammenhang mit einer Performanzverbesserung stehen. Vierzehn Probanden (Lerngruppe) wurden in einwöchigem Abstand zweimal mit dem experimentellen Paradigma im fMRT untersucht und zwischendurch an fünf konsekutiven Tagen mit der Tonhöhengedächtnisaufgabe trainiert. Die Kontrollgruppe (n =10) wurde zweimal gescannt jedoch nicht trainiert. Die Lerngruppe wurde, basierend auf einer Clusteranalyse der Performanzverbesserungsdaten, in eine “starke” Lerner und eine “schwache” Lerner Gruppe unterteilt.

Die post-training und prä-training Bilder für die Gruppe der starken Lerner wurden miteinander kontrastiert und es zeigten sich sowohl positive Signalveränderungen in auditorischen Regionen in der linken Hemisphäre, als auch negative im bilateralen superioren Parietalkortex. Nach dem Training konnte in der Gruppe der schwachen Lerner vermehrte Aktivierung im Gyrus lingualis, Gyrus hippocampalis und in

inferioren Frontalregionen festgestellt werden. Des weiteren wurden negative Signalveränderungen im anterioren Gyrus cinguli beobachtet. Wurden die post versus prä Kontrastbilder zwischen den beiden Gruppen kontrastiert, so konnte eine signifikante Aktivierung des SMG in der Gruppe der starken Lerner im Vergleich zur Gruppe der schwachen Lerner nachgewiesen werden. Der Gyrus supramarginalis scheint eine bedeutende Rolle beim Lernen der Tonhöhengedächtnisaufgabe einzunehmen, was sich vor allem im engen Zusammenhang der Signalveränderung des SMGs mit der Performanzverbesserung wiederspiegelt.

Zahlreiche Studien konnten funktionelle Unterschiede zwischen Musikern und Nicht-Musikern in perisylvischen Region für verschiedene experimentelle Paradigmen aufzeigen. Mehr musikalische Erfahrung war typischerweise mit verstärkter linkshemisphärischer Aktivierung assoziiert. Es bleibt trotzdem unklar, ob diese Gruppeneffekte auf Unterschiede in der Aufgabenperformanz, in kognitiven Strategien oder anatomischer Strukturen zurückzuführen sind.

Studie C untersuchte Unterschiede in der Tonhöhengedächtnisaufgabe zwischen Musikern und Nicht-Musikern. Beide Gruppen zeigten bilaterale Aktivierungen im Gyrus temporalis superior, im SMG, im Gyrus frontalis inferior und Gyrus frontalis medius und im Gyrus parietalis superior. Musiker (im Vergleich zu Nicht-Musikern) zeigten mehr Aktivierung im STG und im SMG. Nicht-Musiker (im Vergleich zu Musikern) aktivierten mehr den rechten primären und den linken sekundären auditorischen Kortex. Aufgrund der identischen Performanz in beiden Gruppen lassen sich die Ergebnisse am ehesten auf Verarbeitungsunterschiede zwischen den beiden Gruppen zurückführen, die wahrscheinlich in engem Zusammenhang mit dem musikalischen Training in der Musikergruppe stehen. Nicht-Musiker aktivieren mőglicherweise eher Hirnregionen die wichtig für Tonhöhendiskrimination sind, während Musiker vorzugsweise jene Hirnregionen aktivieren, welche auf Kurzzeitgedächtnis und Abruf spezialisiert sind.

Trotz dieser Ergebnisse bleibt es unklar, ob die gezeigten Unterschiede zwischen Musikern und Nicht-Musikern auf hirnstrukturelle Unterschiede oder musikalisches Training zurück geführt werden können.

Studie D wurde entwickelt um genau diese Fragestellung näher zu untersuchen. In dieser Studie wurde die Gruppe der starken Lerner der Studie B (n=7) mit einer Gruppe von vierzehn Musikern verglichen, die in punkto Performanz und Geschlecht mit der Gruppe der starken Lernenr übereinstimmte und ebenfalls zuvor

mit dem experimentellen Paradigma getestet worden war. Vor dem Training zeigten zum einen die Nicht-Musiker im Vergleich zu den Musikern erhöhte Aktivierung des linken primären auditorischen Kortex und zum anderen die Musiker im Vergleich zu den Nicht-Musikern erhöhte Aktierung des SMGs.
Der Vergleich nach dem Training zeigte zwar eine Annäherung der Aktivierungsmuster, jedoch wiesen die Nicht-Musiker eine erhöhte Aktivierung des linken Temporallappens auf. Ein signifikanter Performanzunterschied konnte vor jedoch nicht mehr nach dem Training nachgewiesen werden. Das Training führte somit zu einer verstärkten Aktivierung des linken auditorischen Kortex. Aufgrund dieser Ergebnisse lässt sich interpretieren, dass funktionelle Unterschiede zwischen Musikern und Nicht-Musikern teilweise durch Training erklärt werden können.

Darüber hinaus haben einige Studien anatomische Geschlechterunterschiede in sprachrelevanten Hirnarealen nachweisen können. Funktionelle Studien konnten diese Ergebnisse bestätigen indem sie Geschlechterunterschiede in der Sprachverarbeitung aufzeigten, wobei Frauen eine geringere Lateralisierung aufwiesen. Geschlechterunterschiede im Tonhöhengedächtnis könnten ähnliche Ergebnisse zeigen, aber bisher wurde noch keine entsprechende Studie durchgeführt.

Studie E untersuchte mögliche Geschlechterunterschiede in der hemisphärischen Verarbeitung der Tonhöhengedächtnisaufgabe. Geschlechterunterschiede konnten in bilateralen anterioren und posterioren perisylvischen Arealen über den gesamten Zeitverlauf der Aufgabe gezeigt werden. Männer zeigten erhöhte links-lateralisierte Aktivierung in anterioren und posterioren perisylvischen und bilateralen zerebellaren Hirnregionen. Frauen zeigten im Vergleich zu Männern erhöhte Aktivierung des cingulären Kortex. Trotz verschiedener Aktivierungsmuster konnten keine Performanzunterschiede zwischen den Geschlechtern festgestellt werden. Diese Ergebnisse zeigen, dass, wie bereits in der Sprachdomäne nachgewiesen, Männer auch für eine Tonhöhengedächtnisaufgabe eine mehr links-lateralisierte Verarbeitungsstrategie aufweisen.

Verschiedene Studien konnten den Einfluss von Schlaf auf visuelles and motorisches Lernen nachweisen. Der Einfluss von Schlaf auf das auditorische Lernen wurde bisher noch nicht untersucht.

Studie F wurde entwickelt um den Einfluss von Schlaf auf die Performanz im auditorische Lernen zu untersuchen. Sechsundfünfzig Probanden wurden zufällig zwei Gruppen zugeordnet. Verhaltensdaten in der Tonhöhengedächtnisaufgabe

wurden dreimal innerhalb von 24 Stunden erhoben. Die Morgengruppe (MG) wurde zunächst um 9 Uhr morgens und dann wiederholt um 21 Uhr am selben Tag und erneut um 9 Uhr am darauf folgenden Tag (nach einer Schlafperiode) getestet. Die Abendgruppe (EG) wurde erstmals um 21 Uhr und dann am nächsten Morgen um 9 Uhr (nach einer Schlafperiode) und zuletzt um 21 Uhr am selben Tag getestet. Alle Probanden zeigten unabhängig von ihrer Gruppenzugehörigkeit nur eine signifikante Verbesserung nach der Schlafperiode und nicht nach der zwölfstündigen Wachperiode. Demnach scheint Schlaf auch bei der Konsolidierung einer auditorischen Gedächtnisaufgabe eine bedeutende Rolle zu spielen.

Zusammenfassend betrachtet konnte diese Arbeit einen wichtigen Beitrag zur bisherigen Forschung leisten und wichtige Ergebnisse sowohl hinsichtlich des Zeitverlaufs der funktionellen Anatomie des Tonhöhengedächtnisses, als auch training-induzierter Aktivierungsveränderungen und nicht zuletzt hinsichtlich des Einflusses von musikalischer Erfahrung, Geschlecht und Schlaf auf die auditorische Informationsverarbeitung und das auditorisches Lernen aufzeigen. Diese Studien zeigen erstmals, dass der SMG und das Zerebellum eine zentrale Rolle bei der fehlerfreien kortikalen Verarbeitung der Tonhöhengedächtnisaufgabe spielen und darüber hinaus unterstreichen die hier präsentierten Studien die Notwendigkeit, Verhaltensdaten in die Analyse funktioneller Daten zu integrieren.

Zusätzlich konnten die hier präsentierten Daten in ein von Petersen et al. (1998) entwickeltes theoretisches Modell integriert werden. Dieses Modell versucht den Einfluss von Trainingseffekten auf die funktionelle Anatomie der entsprechenden Aufgaben zu erklären.

Darüber hinaus bedarf es weiterer theoretischer und empirischer Forschungsarbeiten zu diesem Themenbereich, um den Zusammenhang zwischen kortikaler Plastizität und auditorischem Lernen weiter zu spezifizieren.

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List of abbreviations

AEF = **auditory evoked fields**
ANOVA = **analysis of variance**
AP = **absolute pitch**
BOLD = **blood oxygen dependence level**
DLPFC = **dorsolateral prefrontal cortex**
EEG = **electroencephalography**
EG = **evening group**
EPI = **echo planar imaging**
ERP = **event related potentials**
FDR = **false discovery rate**
FMRI = **functional magnet resonance imaging**
FMRT= **funktionelle magnetresonanz tomographie**
FWHM = **full width half maximum**
GLM = **general linear model**
HG = **Heschl's gyrus**
HRF = **hemodynamic response function**
Hz = **hertz**
ICBM = **International Consortium for Brain Mapping**
ITP = **imaging time point**
LTD = **long term depression**
LTP = **long term potentiation**
MEG = **magnetencephalography**
MG = **morning group**
MMF = **mismatch field**
MMN = **mismatch negativity**
MMNm = **magnetic mismatch negativity**
MNI = **Montreal Neurological Institute**
MR = **magnet resonance**
MRI = **magnet resonance imaging**
NMR = **nuclear magnet resonance**
PC = **personal computer**

PET = **positron emission tomoragphy**

PT = **planum temporale**

REM = **rapid eye movement**

RF = **radio frequency**

ROI = **region of interest**

SD = **standard deviation**

SMA = **supplementary motor area**

SMG = **supramarginal gyrus**

SNR = **signal to noise ratio**

SPM = **statistical parametric mapping**

SSS = **Stanford Sleepiness Scale**

STG = **superior temporal gyrus**

STS = **superior temporal sulcus**

TE = **echo time**

TR = **repetition time**

TTL = **transistor to transistor logic**

VBM = **voxel based morphometry**

I. THEORETICAL PART

1. The physiological basis of hearing

1.1 Physiology of the auditory pathway

Compared to the visual system, the auditory system consists of a more diffuse network of pathways. Nonetheless, similar to the visual system, the auditory system can generally be broken down into primary and secondary subsystems. The following sections will discuss the functional characteristics of the different levels of the auditory central nervous system, particularly the auditory cortex (Figure 1).

Auditory signals from each ear first reach the Cochlear Nuclei in the respective hemispheres via auditory nerve fibers. These nuclei, referred to as the ventral and the dorsal nucleus, are located on each side of the medulla. Each auditory nerve fiber splits to project in both nuclei. Organized into subdivisions, which can be identified by morphologically distinct cells, these nuclei show specific frequency response characteristics. Low frequency sound waves are processed in the ventral, rostral, and lateral parts of each cochlear nucleus, while the dorsal, caudal and medial subdivisions respond to high frequency sound waves. From the cochlear nuclei, the majority of auditory fibers project in the superior olivary complex, a group of nuclei, which is also located in the medulla. Each of the superior olive receives projections from both the ipsilateral and contralateral cochlear nucleus. Because the contralateral projections are larger than the ipsilateral, the primary auditory cortex primarily receives information from the ear of the contralateral side of the head.

According to research findings, the medial and lateral superior olive nuclei play an important role in sound localization (for review see e.g. Tollin, 2003; Grothe & Park, 2000). The medial superior olive nucleus responds to small time differences of sound arrival at each ear (time difference) and lateral superior olive nucleus processes amplitude differences of sound waves reaching each ear (phase differences). This information is subsequently transformed in an auditory spatial map located in the inferior colliculus.

Arising from the superior olivary complex, fibers project through the lateral lemniscus tract to the inferior colliculus, which is a component of the tectum of the dorsal midbrain. From the inferior colliculus, two distinct pathways project to the ventral and dorsal regions of the medial geniculate nuclei of the thalamus. While

projections from the dorsal medial geniculate nucleus reach the secondary auditory cortex, regions from the ventral part of the medial geniculate nuclei project to the primary auditory cortex. The medial nucleus also projects to subcortical structures in the frontal lobe as well as the dorsal amygdale and the posterior neostriatum. In order to assess the role that these connections play, for instance, in emotional responses to auditory input, extensive research has been conducted on this subject (Hennevin et al., 1995, 1998; Poremba & Gabriel, 1997).

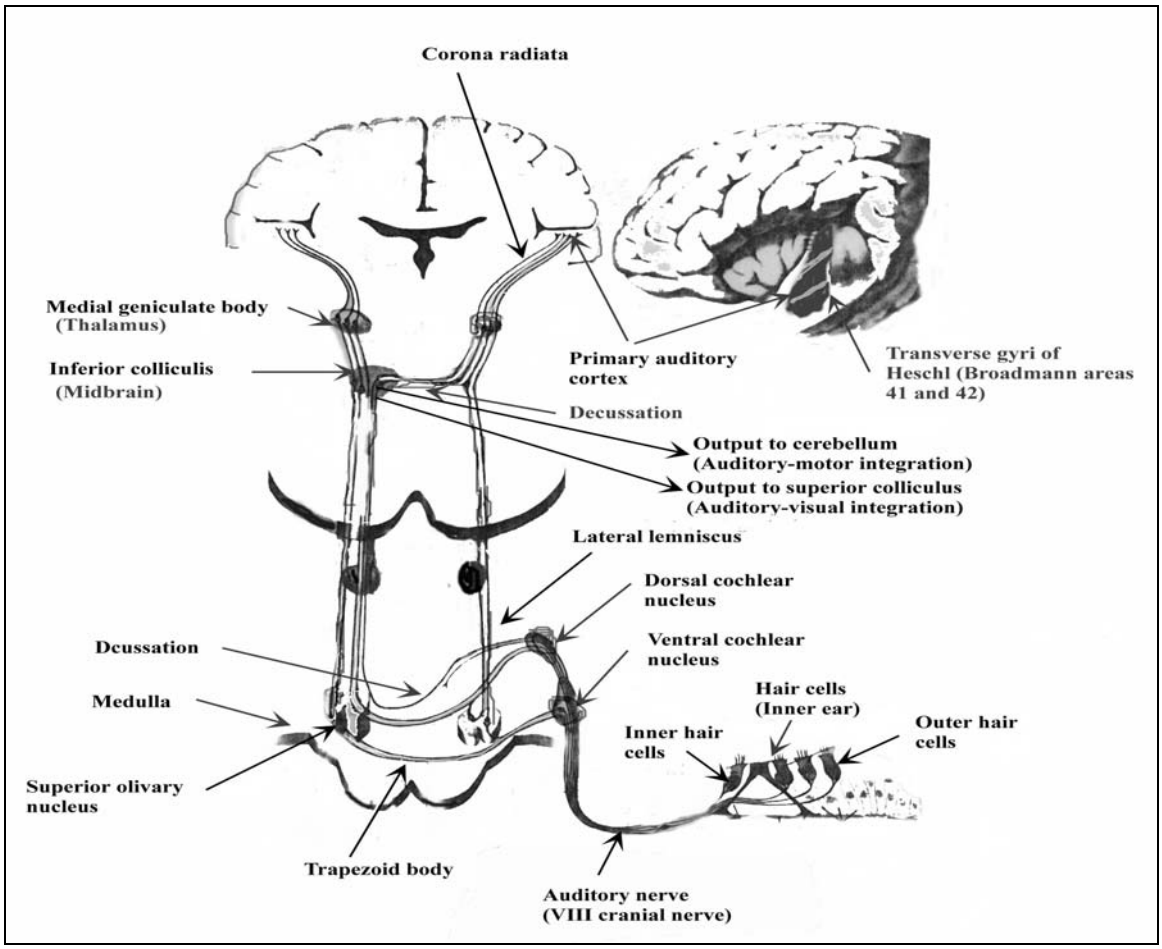

Figure 1: Physiology of the auditory pathway (http://www.public.iastate.edu/~cmdis470/sensorymotorsystems/auditory_pathway.html)

1.2. The anatomy of the auditory cortex

The projections from the medial geniculate nucleus to auditory areas of the cortex are the final output from the auditory pathways. In all mammals the auditory cortex lies in a subsylvian position. For primates in particular, it is more or less buried in the sylvian fissure. Based on studies assessing the cytoarchitectonic subdivisions in the

auditory areas (von Economo & Horn, 1930; Galaburda et al., 1978; Galaburda & Sanides, 1980; Morosan et al., 2001; Rademacher et al., 2001), three distinct subdivisions were defined: the primary auditory cortex, the secondary auditory cortex and auditory association areas (tertiary auditory cortex).

1.2.1. The primary auditory cortex

The primary auditory cortex is located inside the lateral fissure along the ventral surface of the superior temporal lobe (Figure2). The small transverse gyrus in the superior temporal lobe that contains the primary auditory cortex is often referred to as Heschl's gyrus, AI, or Brodmann's (Brodmann, 1909) area 41 (central primary auditory region). The primary auditory system contains neurons that respond to a frequency range from 20-20.000Hz and register the characteristics of sound identification or perceptual processing, such as loudness, pitch and timbre. The response of neurons in the primary auditory cortex to specific sound wave frequencies is narrow and binaural (Reser et al., 2000; Schreiner et al., 2000). Some neurons are excited by both ears while others are excited by stimulation from one ear and inhibited by stimulation from the other. The primary auditory cortex is organized in vertical columns. The cells in each column are sensitive to a similar main sound frequency and neighboring columns are organized according to the tonotopic representation (see section 1.3.1).

1.2.2. The secondary auditory cortex

The primary auditory cortex is surrounded by the secondary auditory cortex, which receives projections from the primary auditory cortex (Figure2). Covering the superior edge of the lateral surface of the temporal lobe, this region corresponds to the Brodmann areas 42 (auditory core region at the medial, rostral and caudal border of 41) and 22. The planum temporale (PT) is one of the main regions of the secondary auditory cortex and covers primarily Brodmann area 42 with a small part reaching into Brodmann area 22. Although the PT was originally thought to be predominately involved in language functions, recent functional studies confirmed the involvement of the PT in several other functions, including general sound and music processing (see also sections 1.3.1. and 1.3.3). The PT is located on the superior surface of the temporal lobe within the sylvian fissure and has a sheet-like, almost triangular structure. While numerous studies have been conducted in an attempt to define the

borders of the PT, their findings have been somewhat inconsistent (e.g. Pfeifer, 1920; Galaburda et al., 1978; Galaburda & Sanides 1980; Steinmetz et al., 1990,a,b, 1991; Jancke et al., 1994). Shapleske et al. (1999) reviewed the existing literature regarding the PT and suggested some guidelines regarding the anatomical borders of the PT.

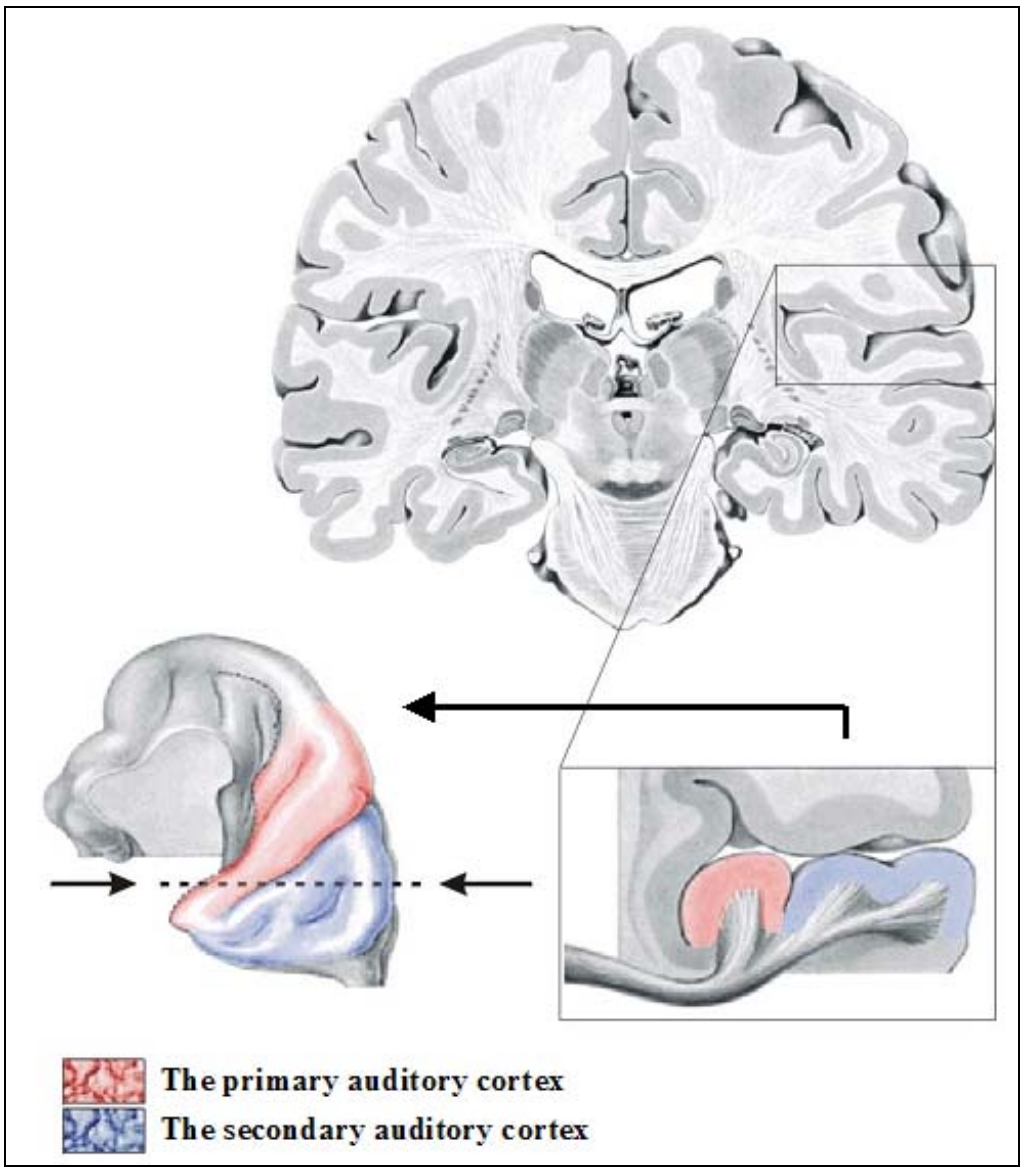

Figure 2: The primary and secondary auditory cortex (modified from Nieuwenhuys et al. 1998)

Furthermore, the authors provide an overview about the size of the PT as well as influences of gender and handedness on size and asymmetry of the PT. In their meta-analysis of 22 studies, Shapleske et al. (1999), noted that a leftward asymmetry of the area of the PT has been found in most studies and applies to approximately 78% of

the measured subjects. The PT's of several clinical populations, including schizophrenics and dyslexics, exhibit structural and functional differences in the PT compared to a normal population. A few studies showed an increased left-warded asymmetry of the planum temporale in professional musicians with absolute pitch (Schlaug et al., 1995a,b; Zatorre et al. 1998; Keenan et al., 2001).

1.2.3 Auditory association areas (tertiary auditory cortex)

The tertiary auditory cortex, which roughly corresponds to Brodmann area 22, is located on the superior temporal gyrus (STG) and the superior temporal sulcus (STS) within the temporal lobe. Also known as the auditory belt regions, both areas lie lateral and ventral to the primary auditory cortex. The auditory association cortex of the STG projects to the multimodal cortex of the STS, and the STS also receives projections from somatosensory and visual areas (e.g. Baylis et al, 1987; Desimone & Ungerleider, 1986). Several studies, some of which are discussed in section 1.3, assessed the multiple roles of the tertiary auditory cortex in auditory information processing (e.g. Cansino et al., 1994; Binder et al., 1994, 1996, 1997, 2000; Zatorre et al., 1992; Demonet et al., 1992; Jancke et al., 2002b).

Furthermore, some studies provide evidence for the involvement of frontal, parietal and cerebellar areas in auditory processing. According to a cytoarchitectonic study by Galaburda & Sanides (1980), auditory-related cortex exists in the parietal operculum and the inferior parietal lobule. Romanski & Goldman-Rakic (2002) recorded neuronal responses to auditory cues from the ventrolateral prefrontal cortex in awake monkeys. The localization of auditory responses in the ventral prefrontal cortex in the macaque brain is suggestive of some functional similarity between this region and the inferior frontal gyrus of the human brain (including Broca's area), where mnemonic, semantic and syntactic auditory processes have been shown to lead to brain activation (see section 1.3).

Research studies assessing the auditory regions have surveyed the entire life span from infancy to late adulthood (Abdala & Sininger, 1996; Boothroyd, 1997; Pasman et al., 1999). During the first year of life, neurons in the brain stem and important neuronal connections between brain stem nuclei, thalamic nuclei and auditory cortex are formed, resulting in the rapid development of auditory functions in infants (e.g. Nara et al., 1993; Peck, 1995; Rubsamen, 1992). If sensory input is not provided or

hearing is impaired during those early stages of development, the morphology and function of the auditory pathway can be severely affected.

Not only have studies assessed the basic principles of auditory processing in animals and humans, but current research programs using various methods focus on the neuronal changes accompanying recovery of auditory function following system damage (e.g. following cochlear implants; Manrique et al., 1999; Nishimura et al., 2000; Ponton, et al., 1999; Robinson, 1998; Shepherd et al., 1997), the effects of training and deprivation on neuronal plasticity, and neurochemical mechanisms involved in plasticity. The following sections (1.3 and 2) will provide a brief overview concerning this body of research.

1.3 The functional anatomy of the auditory cortex

Many studies have been conducted in order to assess the functional organization of the auditory areas in mammals including non-human primates (for detailed reviews see Bonin & Bailey, 1947; Bailey et al., 1950; FitzPatrick & Imig, 1978; Aitkin & Martin, 1990; Kaas & Hackett, 1998; Rauschecker, 1998a,b; Schreiner 1992, 1998). Most of these studies examine tonotopy and amplitopy of the auditory regions. When compared to animals, humans were shown to process additional complex sound patterns, such as language or music. The following section will provide a brief overview regarding the functional anatomy of the human auditory cortex.

1.3.1 Auditory perception

1.3.1.1. Tonotopy of the human auditory cortex

Much like other areas of the cerebral cortex, the auditory cortex is organized in functional columns. Within the auditory cortex, different sound frequencies are represented in particular regions. In this arrangement, referred to as *tonotopic representation,* higher frequencies are located in more anterior mesial regions while the posterior lateral regions responding to lower frequencies. Whereas tonotopic representation has been well examined in various animal species, tonotopy in the human auditory regions continues to be a matter of controversial debate since relatively little is known about it. Pantev et al. (1995), revealed a tonotopic representation across the supratemporal surface with auditory evoked potentials in

humans. The region responding to higher frequency stimuli is found to be located deeper within the lateral fissure and closer to the mediosagittal plane.

Several fMRI studies confirm the tonotopic principle in humans (e.g. Strainer et al., 1997; Hart et al., 2003a,b). Additionally, Bilecen et al. (1998) found that activated areas for high frequencies of about 4000Hz were located more frontally and medially as compared to low frequencies (500Hz). Nevertheless, there is a high interindividual variability of the Heschl's gyrus, which makes it difficult to compare individual tonotopic maps (Schonwiesner et al., 2002). The use of various different methods may cause more problems. In a recent study, Lutkenhoner et al. (2003) stated that studies of tonotopy based on wave N100 of the auditory evoked field were found to be problematic. This problem is only exacerbated by the hypothesis that there may be several tonotopic maps represented in the human auditory cortex, each with specific functions in demodulation of speech and other complex sounds.

1.3.1.2 Amplitopy of the human auditory cortex

In addition to studies assessing tonotopic representation in the human auditory cortex, a few studies have investigated a possible amplitopic organization within the auditory cortex (i.e. a spatial distribution of neurons that are maximally responsive to certain stimulus intensities). Using auditory evoked magnetic fields (AEF), Pantev et al. (1989) revealed a possible amplitopic representation Their results were supported by a recent fMRI study, which found that a two-dimensional drift of cortical activation occurred as sound pressure increased (Bilecen et al., 2002). These shifts were observed within Heschl's gyrus from the ventral to the dorsal edge and from the lateral to the medial part. According to the authors, the latero-medial drift mimics the known tonotopic principle of frequency-encoding neurons. Furthermore, the authors argue that their findings corroborate the existence of an amplitopic pattern of intensity-encoding neuronal clusters that resemble the tonotopic representation.

In addition to tonotopy and amplitopy in the auditory cortex, there is some evidence for spatiotopic maps within the auditory region, with sounds from the contralateral hemifield being more excitatory in a given hemisphere as well as the involvement of posterior auditory and parietal regions in sound localization (Zatorre et al., 2002; Griffiths et al., 1998; for a review see Hall et al., 2003). A growing body of research assessing specific temporally sensitive responses within the auditory

cortex suggests that the auditory cortex may play an important role in noise filtering, or possibly even in the processing of virtual pitch (Schulte et al., 2002), timbre or sound localization.

These findings provide important information necessary for the interpretation of higher auditory functions such as complex sound perception or speech. The following section will provide a brief overview regarding the functional anatomy of complex sounds.

1.3.1.3. Auditory processing of complex sounds

The processing of complex sound features is essential for most of the communication among humans. While the perception of environmental sounds, speech and music undoubtedly involves the primary auditory cortex, other secondary auditory and extratemporal regions also seem to play an important role. Although numerous studies have assessed higher-order auditory functions and processing of complex tones in the human brain, only a few can be named and discussed here (for reviews see e.g. Griffiths et al., 1999a,b, 2001; Rauschecker, 1998b).

Using psychophysical studies of neurological patients as well as PET and fMRI in normal subjects, Griffiths (1999a,b) examined brain areas involved in the analysis of auditory space and timing information in the auditory system, respectively. These studies revealed brain mechanisms for auditory spatial and timing information, which are distinct from areas involved in frequency processing. The presented and discussed imaging data suggest a network involving bilateral frontal and right parietal areas for the perception of auditory movement in space. Zatorre at al. (2002) examined the functional characteristics of auditory regions involved in sound localization and found that posterior auditory cortex seems to process sounds that vary in their spatial location. It was argued that the right inferior parietal cortex also plays an essential role in sound localization and behavioral scores could be predicted from the activity intensity in this region. These studies provide support for the hypothesis that extratemporal brain regions are involved in analysis even at a perceptual auditory level. In a subsequent paper, Griffiths (2001) provides evidence for the existence of a hierarchal organization of the neural substrates for the processing of sound sequences. Based on his research, the author suggests that the spectrotemporal features of individual sounds are processed within the pathway up to and including the primary

auditory cortices. Bilateral temporofrontal networks seem to be involved in subsequent higher-order temporal processing of these individual sounds.

There is also a growing body of literature, which assesses laterality effects in the brain in response to auditory stimuli. While it is well known that language shows a left hemispheric predominance, some evidence suggests a right shifted network for music processing. However, this subject is still a matter of debate (see also section 1.3.3). The functional anatomy of language is well examined, and several recent reviews provide a detailed overview (e.g. Wise, 2003; Friederici, 1995, 1997; Matthews et al., 2003; Small& Burton, 2002; Grodzinsky, 2002; Bookheimer, 2002). In a review article, Patel (2003) links and compares the language and music research literature. Sections 1.3.2 and 2.3.2 will further discuss some of the findings regarding music processing in non-musicians and musicians.

Studies have also found atypical processing of complex sounds in several populations, including dyslexics and schizophrenics (e.g. Temple, 2002; Breznitz & Meyler, 2003; Backes et al., 2002; Heiervang et al., 2002; Godoy et al., 1990; Hajek et al., 1997a,b; McCarley et al., 1993), and further research will hopefully lead to the development of appropriate interventions, including intensive training for these groups.

1.3.2 Music processing in non-musicians

Some of the current research on the physiological basis of hearing in animals and humans has been discussed in the previous sections. Although animals can perceive small sound differences, they appear to be unresponsive to the holistic aspects of music. Music processing is not a simple sum of auditory processing and auditory memory (see section 1.3.3). It can be experienced physiologically (e.g. through emotions) and cognitively as a result of e.g. musical knowledge and expertise as well as personal memories. A growing body of research assesses the functional anatomy of music processing. While a forthcoming section will discuss the influence of musicianship on auditory processing (see section 2.3.2), this section will focus on processing of musical features in non-musicians.

In 1994, Zatorre and colleagues investigated the neural correlates of music perception using PET. In this study, subjects were asked to perform four different tasks. They had to either (a) listen to a sequence of noise bursts (control task), (b) listen to unfamiliar tonal melodies (passive listening), (c) compare the pitch of the

first two notes of the same set of melodies (low auditory memory load) and (d) compare the pitch of the first and last notes of the melodies (high auditory memory load). Among other findings the authors discovered that passive listening to melodies resulted in activation of right superior temporal gyrus (STG) and occipital areas. When compared with the passive listening condition, the low memory load condition revealed right hemispheric frontal lobe activation. The study also revealed that both memory conditions resulted in decreased activity in the left temporal lobe. The authors of this study concluded that the right superior temporal cortex plays an important role in the perceptual analysis of melodies, while the right frontal lobe seems to be involved in pitch comparisons and the active retention of pitch.

As section 1.3.1 indicated, there is an ongoing debate about a possible right hemispheric preference for music processing. The above-described study gains support from a study by Griffiths et al. (1999a). When subjects were asked to make a same/different judgment while comparing pitch sequences of 6 tones, a more extensive right lateralized network including cerebellar, posterior temporal and inferior frontal regions was found. Nevertheless, there is also evidence for the involvement of left temporal areas in music perception and processing. For instance, Platel et al. (1997), revealed more left hemispheric activations involving the precuneus, superior temporal and superior frontal gyrus when subjects were asked to detect pitch changes in familiar tunes. When subjects were presented with deviances in tonal sequences, Celsis et al. (1999) showed rightward asymmetry of the primary and secondary auditory cortex for tones, but left more than right posterior temporal lobe activation for the deviant condition. This brief overview illuminates the need for further more detailed assessments of hemispheric preferences in processing of certain musical features.

In order to investigate whether non-musicians have “musical knowledge”, Koelsch et al. (2000) asked subjects listen to chord sequences, which infrequently contained a chord violating the sound expectancy of listeners. Using event-related brain potentials (ERPs), the authors found that the amplitudes of the early and late bilateral-frontal negativities were sensitive to both the degree of the probability for deviant acoustic events and musical expectancy, which was induced by the preceding harmonic context. Along with subsequent studies by the authors, this suggested that even non-musicians show a passive learned or predispositional knowledge for musical pattern. A similar effect could also be seen in children age five (Koelsch et al., 2003),

and Trehub and colleagues revealed certain musical predispositions in infancy in numerous studies (e.g. Trehub et al., 1984, 1999; Morrongiello et al., 1985; for reviews see Trehub 2001, 2003). These predispositions could also be found for speech sounds (for review see Trehub et al., 1993).

Music and language are both specific to humans and both are complex in structure and are based on certain rules. Using a variety of tasks comparing music to speech, several studies from various fields have assessed the similarities and differences between music and language in neurologically impaired patients and normal volunteers (e.g. Besson et al., 1998; Palmer & Kelly, 1992; Patel et al., 1998a,b; Tervaniemi et al., 1999, 2000; Crawley et al., 2002; Maess et al., 2001; Balter, 2001; Hebert & Peretz, 2001; Hebert et al., in press; Perry et al., 1999; Schon et al., 2002). These studies focus on the shared aspects of music and language, such as pitch prosody, melody, rhythm and syntax, as well as the unique facets of each. One interesting model was recently introduced by Peretz & Coltheart (2003). The authors discussed the existence of a "music-processing module" in the brain and provided an overview of brain-damaged patients who showed selective impairments in music recognition but preserved language capabilities. According to the authors, these studies provide strong evidence for the existence of distinct and separate processing modules (e.g. language and music) within a general auditory processing system. The authors also suggest that these two systems process incoming auditory stimuli in parallel and that the "activation of the music or the language processing modules is determined by the aspects of the input to which a module is tuned".
Nevertheless, there is a lack of studies assessing distinct or shared neural networks for the three subcategories - language, music and environmental sounds - within the proposed overall auditory module.

One other important aspect of music processing is the emotional aspect, but the neural correlates of the accompanying emotional response to music are barely investigated. In a study that assessed affective responses to music, a novel musical tune was varied systematically in the degree of dissonance. Covariations in blood flow changes were revealed in paralimbic and neocortical regions as a function of induced dissonance and reported pleasantness/unpleasantness. The authors concluded that the activated brain regions are similar to previous reported regions activated in pleasant/unpleasant emotional states (Blood et al., 1999). In a subsequent study, Blood & Zatorre (2001) investigated the neural correlates of music that elicited the

highly pleasurable experience of "shivers-down-the-spine" or "chills." Cerebral blood flow increases and decreases were observed in brain regions which are known to be involved in reward, motivation, emotion and arousal and which typically respond to “pleasure” inducing stimuli, such as food, sex, and certain drugs. While these studies suggest that music might be associated with other survival-related stimuli in humans, further studies are needed in order to identify specific emotions in response to music.

There is also a body of research concerning the effects of brain damage on music processing (e.g. musical agnosia or amusia). Strokes, traumatic brain damage, and congenital brain anomalies can lead to various disorders of music processing (e.g. Liegeois-Chauvel, 1998; Tramo & Bharucha, 1991; Peretz et al., 2001; Samson et al., 2002). Recent studies focus especially on the behavioral and neural correlates of congenital amusia (e.g. Ayotte et al., 2002; Stewart & Walsh, 2002; Peretz & Hyde, 2003). These studies provide important evidence for the localization and identification of neural networks subserving musical processing in general as well as processing of specific musical features.

In addition to the processing of certain musical sound components, the investigation of the influence of music on emotions and important insight from studies assessing brain lesion and congenital disorders, several studies have been conducted in order to examine certain memory systems for the auditory and music domains. In a recent study, Platel et al. (2003) investigated a possible distinction between semantic and episodic memory of music using high-resolution PET. In the semantic memory condition, subjects had to decide whether or not a musical tune was felt “familiar”. In order to study episodic memory, the authors designed two delayed recognition tasks, which contained either familiar or unfamiliar tunes. Bilateral activation of the superior frontal gyri and the precuneus were observed in the episodic task, while the semantic task activated bilateral orbitofrontal, the left angular gyrus and the left hemispheric middle temporal gyrus. According to these results, there appear to be two distinct neural networks for semantic and episodic memory systems for music.

The following section will address studies regarding additional auditory memory systems, such as auditory short-term memory and auditory sensory memory (echoic memory).

1.3.3. Auditory short-term and echoic memory

One important feature of the human auditory system is the auditory memory, which involves the abilities to perceive and process information that is presented acoustically, including voice, environmental sounds, music and other complex sounds. This information must be stored in memory and recall should occur intentionally as well as unintentionally. Auditory memory involves several tasks, including attending, listening, processing, storing and recalling, being performed successfully as well as often simultaneously. Most of the research regarding auditory sensory memory has been conducted in the field of psychophysics. Psychophysical theories distinguish between auditory sensory (echoic memory) and auditory short-term memory. By definition, echoic memory is a system that receives auditory stimuli and maintains them for a short period of time in sensory stores, and therefore represents the earliest stages of sensory memory. Numerous behavioral and psychophysical studies have assessed the specific features of echoic memory (e.g. Neisser, 1967; Darwin et al., 1972, Cowan, 1984). Sensory memory appears to permit the trace of a stimulus to "remain" for additional processing, which might be necessary to integrate information across time and space and select important stimuli for further processing. In studies assessing echoic memory, findings suggest a similarity between echoic memory and its visual counterpart, the iconic memory. Although echoic memory lasts approximately four seconds while iconic memory lasts only one second, the echoic memory does not preserve as much information as the iconic memory system (echoic: 4-5 items; iconic: 8-9 items).

Currently, a common method for examine auditory sensory memory is the mismatch negativity (MMN). During the late 1970s, several studies found that the MMN was elicited following the presentation of a deviant tone in an otherwise consistent stimulus sequence. Naatanen et al. (1978) suggested that the MMN is generated by a neuronal mismatch between the deviant sensory input and a sensory memory trace, which represents a preceding repetitive auditory stimulus. Because the MMN can also be recorded in an inattentive state, echoic memory mechanisms seem to operate without attention-related cognitive processes. Since MMN generators can be localized in the brain, neural correlates and brain areas of auditory sensory memory can be identified. Although the features of echoic memory closely resemble the memory system reflected in the MMN, there is an ongoing debate regarding whether the MMN can be considered as the physiological correlate of echoic memory (e.g.

Naatanen et al., 1989a,b; Jaaskelainen et al., 1999). Further research is thus necessary to clarify this issue. During the last 10 years, the MMN and its magnetic counterpart, the MMNm has been used to investigate wide research interests, such as complex sounds (e.g. Schroger et al., 1994; Alho et al., 1996; Ioannides et al., 2003), speech and language features in adults and newborns (e.g. Winkler et al., 1999; Cheour et al., 2002), music (Tervaniemi et al., 1997; see also section 1.3.2.), and sensory memory deficits in various clinical populations (for a review see Naatanen & Escera, 2000; Naatanen, 2003).

While there is no doubt as to whether the MMN is a useful method for assessing auditory sensory memory, it is difficult to observe a functional network of auditory memory using this method.

A few PET and fMRI studies have assessed the functional anatomy of pitch memory and auditory working memory in humans, but research conducted to date has not revealed a consistent functional pattern involved in auditory memory. It seems unclear which brain regions are involved and whether they are involved successively or simultaneously. There are also some discrepancies between the animal and the human literature regarding preserved auditory memory functions after retention or lesions within the temporal lobes. Weinberger (1998) provides an overview regarding the animal literature, and chapter 7 of this paper also provides a brief introduction to this issue.

In addition to evidence regarding auditory short-term and echoic memory, there are some studies that demonstrate compensatory performance changes in long-term auditory memory functions as a result of the loss of the sensory visual system. Roder and colleagues revealed improved verbal memory as well as memory for environmental sounds in congenitally and late blind adults (Roder et al., 2001; Roder & Rosler, 2003). Blind people have to rely more on auditory input in order to cope with daily life and acquire auditory information about their environment. These studies provide important evidence for the high adaptive capability of the human brain. The following chapter will provide an overview about studies that have assessed cellular, structural and functional plasticity in the brain.

2. Plasticity and the brain

The term cortical plasticity refers to enduring changes in cortical properties such as strength of synaptic connections, altered representational patterns or networks including reorganization of neural connections. Such changes can be either morphological or functional. For many years plasticity has been accepted as a phenomenon involved in synaptic strength modifications of the developing brain. However, over the last two decades neurophysiological and neuroanatomical studies in animals and noninvasive methods (e.g. fMRI, and EEG) in humans have provided evidence that the adult cortex is also capable of plasticity. Generally, one can say that periods of rapid change or plasticity occur in the brain in four main conditions:

a) sensory information processing in the immature brain (developmental plasticity)
b) changes in the body that modify the balance of sensory activity received by the brain (activity-or use-dependent plasticity)
c) behavioral alterations based on new information or training (plasticity of learning and memory; experience-dependent plasticity)
d) damage to the brain (injury-induced plasticity).

Those changes can either occur on the cellular and molecular level or on the network level, and categorization is often difficult. A brief overview of plasticity and possible influencing factors will be given in the subsequent sections.

2.1 Cellular mechanisms of synaptic plasticity

To date, a large body of experimental results regarding synaptic plasticity has been revealed. Most of these experiments are inspired by Hebb's postulate (Hebb, 1949) that describes how the connection from presynaptic neuron A to a postsynaptic neuron B might be modified.

"When an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased." (Hebb, 1949).

Thus, while the change at a synapse s_{xy} is dependant on the state of the presynaptic neuron x and the postsynaptic neuron y and the present efficacy s_{xy}, this change does not dependent on the state of another neuron n.

Formulated on purely theoretical grounds, this postulate is often rephrased in the sense that modifications in the synaptic transmission efficacy are driven by correlations in the firing activity of pre-and postsynaptic neurons. Although James (1890) first expressed the idea of learning through correlations, correlation-based learning is now generally called Hebbian learning.

Three main components of Hebbian learning will be briefly discussed in this section. However, there are various other learning postulates as well as modification of Hebbs' postulate, which cannot be covered in this section.

2.1.1 Long-term potentiation and depression (LTP, LTD)

Neuron models indicate that each synapse is characterized by a single constant parameter s_{xy} that determines the amplitude of the postsynaptic response to an incoming action potential. More than 20 years after Hebb's postulate was devised, electrophysical experiments revealed that the response amplitude is not fixed and can change over time (Lomo, 1966; Bliss & Lomo, 1973; Bliss & Gardner-Medwin, 1973). Suitable stimulation paradigms (e.g. Bliss & Collingridge, 1993) can systematically induce changes of the postsynaptic response that can last for hours or days. If the stimulation paradigm leads to a persistent increase of the synaptic transmission efficacy, the effect is called long-term potentiation (LTP) of synapses. These changes can be induced by the dual (associative) activity of the presynaptic and postsynaptic neuron, and clearly resemble the mechanism that Hebb proposed earlier (Kelso et al., 1986).

If the result of the dual activity between the presynaptic and postsynaptic neuron is a decrease of the synaptic efficacy (reduction in sensitivity), it is referred to as long-term depression (LTD) (e.g. Morris, 1989, Linden & Conner, 1995). One method for inducing LTD is the stimulation of neocortical and hippocampal presynaptic inputs at low frequencies, e.g. 1-5 Hz for several minutes (Kemp & Bashir, 2001), and activation of a specific synapse without generation of an AP in the postsynaptic neuron is a necessary condition for inducing LTD. These persistent changes are thought to be the neuronal correlate of 'learning' and 'memory' (for reviews see Martinez & Derrick, 1996; Bennett, 2000; Nayak & Browning, 1999; Malenka & Nicoll, 1999).

2.1.3 Spike-time dependent hebbian plasticity (STDHP)

As described in section 2.1.1 for Hebbian learning, a synaptic strength is increased if presynaptic and postsynaptic neurons are 'simultaneously' active. If neurons communicate via spikes, the concept of simultaneity implies that the pre-and postsynaptic spikes occur within some specified period of time. Experimental evidence indicates that synaptic modification can depend upon the timing of presynaptic inputs (excitatory postsynaptic potentials) and postsynaptic spikes (action potentials) (Markram e al., 1997; Bi & Poo, 1998; Zhang et al., 1998; Debanne et al., 1998; Egger et al., 1999). Topics concerning competition between synapses and the stability of the learning algorithms have been a particular focus of attention and have to be further assessed (see e.g. Miller & MacKay, 1994; Miller, 1996; Song et al., 2000, Rao & Sejnowsli, 2001).

2.2 Structural plasticity in the adult brain

The above-described Hebbian learning rules have been used to explain recent findings in animal studies assessing experience-driven neuroplasticity in several domains (Kaas, 1991; Kilgard et al., 2001; Singer, 1995; Recanzone et al., 1993; see also section 2.3). Structural plasticity in animals is frequently investigated by the measurement of the size and temporal organization of cortical representations (e.g. receptive fields, RF) in relation to experience. Recent studies have shown increases or decreases in the size of a receptive field in response to intensive training. Kilgard et al. (2001) found an expansion of receptive fields in the primary auditory cortex in relation to improvement of an auditory temporal order judgment task, whereas others have shown an enlargement of receptive fields in response to an intensive frequency discrimination training (Recanzone et al., 1993). Experience-dependent changes have also been found on the microscopic and macroscopic level (e.g. Anderson et al., 1994, 2002; van Praag et al 1999; Black et al., 1990; Kleim et al., 1996), revealing neuroplasticity, such as glial hyperthrophy, in relation to synaptogenesis after an intensive motor-skill training.

In addition to the animal literature, there is a growing body of literature assessing humans. New non-invasive methods (e.g. voxel-based morphometry (VBM); Ashburner & Friston, 2000; Good et al., 2001a,b) make it possible to investigate structural brain differences between or within certain human populations

in the living brain. These studies could reveal intermodal plasticity in various disorders, such as schizophrenia (e.g. Job et al., 2002; Zhou et al., 2003; Kubicki et al., 2002), narcolepsy (Overeem et al., 2003), Alzheimer (e.g. Karas et al., 2003; Busatto et al., 2003; Burton et al., 2002), dyslexia (Temple & Gabrieli, 2003a; Brambati et al., 2003; Brown et al., 2001), depression (e.g. Steingard et al., 2002; Vythilingam et al., 2002), in relation to language acquisition (Golestani et al., 2002), or in subjects suffering form congenitally sensory loss (Emmorey et al., 2003). Furthermore, these methods will become an important tool for monitoring the effects of stroke and brain injury rehabilitation (Huppi, 2002; Schormann & Kraemer, 2003; Binkofski et al., 2001). In most of these studies, it remains unclear whether the anatomical differences were triggered by the disease or syndrome or whether the illness or at least an increased risk for a clinical manifestation resulted from an anatomical predisposition. Therefore, it is important to differentiate between experience-dependent plasticity, disease- or injury-related plasticity and pre-disposition-related structural differences.

In order to assess experience-dependent plasticity in the human brain, Maguire and colleagues (2000) compared humans with extensive navigation experience (licensed London taxi drivers) with normal control subjects. They found significantly enlarged posterior hippocampi in taxi drivers in comparison to the controls. Furthermore, the hippocampal volume correlated with the amount of time spent as a taxi driver. The results suggest that increased posterior hippocampal gray matter is acquired in response to increased taxi driving experience. The authors interpret their results as a structural change in response to specific environmental demands. Alternatively however, one could hypothesize that the difference in hippocampal volume is instead associated with innate navigational expertise, which could lead to an increased likelihood of choosing a taxi driver career. A follow-up study was designed, which investigated the correlation between navigational skills and hippocampi volume in normal subjects who showed a high variability of navigation expertise (Maguire et al., 2003). There was no significant correlation within these normal subjects, which suggests that structural differences in the human hippocampus are typically not related to spatial representation acquired during life.

Nevertheless, further research, e.g. longitudinal studies, is needed in order to distinguish between experience-related and more predisposition-related influences on the brain (e.g. Schlaug et al., 2003).

2.2.1 Musicianship and structural plasticity

Recently, there has been an increasing amount of literature attempting to link extraordinary skills with changes in human brain anatomy. Professional musicians in particular have been investigated using various methods. There are several reasons why musicians are particularly suitable for assessing experience-dependent plasticity. First, musicians have to practice for a significant amount of time on a regular basis over an extended period of time in order to achieve a certain level of musical expertise, which should increase the likelihood of experience-dependent plasticity. Secondly, some musicians have an early age of commencement, so they begin practicing within the brains' developmental 'critical period' (for review see Rosenzweig, 2003; Hensch, 2003). In addition, while playing music, musicians have to perform complex physical, sensory and cognitive tasks simultaneously.

For the musician group, there is evidence for an increased corpus callosum size (Schlaug et al., 1995a, 2001; Lee et al., 2003; Ozturk et al., 2002), a greater cerebellar volume (Hutchinson et al., 2003; Sluming et al., 2003; Schlaug, 2001); an enlarged volume of the anteromedial portion of Heschl's gyrus (Schneider et al., 2002), and changes in the primary motor cortex (Amunts et al., 1997) and Broca's area in the left inferior frontal gyrus (Sluming et al., 2002). There are also structural differences between musicians with and without absolute pitch (AP) in the planum temporale (PT) (Schlaug et al., 1995b; Keenan et al., 2001; Luders, et al., 2003).

A recent study by Gaser & Schlaug (2003) used voxel-based-morphometry (VBM) in order to assess structural differences across the whole brain between professional musicians, amateur musicians and non-musicians. When comparing the professional musicians with each of the two other groups, the authors could reveal gray matter volume differences in motor, auditory, and visual spatial brain regions.

Nevertheless, there is an ongoing debate over whether these differences are directly related to predisposition or are a result of structural adaptation due to intensive long-term training of auditory, motor and visual spatial abilities (for a review see Munte et al., 2002; Schlaug, 2001; Jancke, 2002a). One strong indicator for experience-dependent plasticity rather than predisposition-related differences in musicians' brains can be cited in the correlation that is often found between the extent of anatomical differences and the age of commencement of musical training (Schlaug et al., 1995a,b, 2001; Keenan et al., 2001; Gaser et al., 2003). These findings support the hypothesis that the anatomical differences between musicians and non-musicians

are related to experience and thus not an effect of predisposition. Brain differences resulting from a strong influence of predisposition should correlate with familial musical ability rather than age of commencement. However, additional studies need to be designed and conducted in order to assess the relationship between anatomical brain alteration in musicians and familial musical abilities.

The study by Gaser & Schlaug (2003) corroborates that experience, rather than predisposition is the primary factor influencing brain differences. In comparison to the professional musicians and the non-musicians, amateur musicians showed an intermediate level of brain changes, which support the hypothesis of experience-related structural plasticity in musicians. Nonetheless, the authors state that self-selection in individuals with a 'music' predisposition cannot be ruled out entirely. A study by Hutchinson et al. (2003) also supports experience-related structural plasticity in musicians. In this study, lifelong intensity of practice correlated with relative cerebellar volume in male musicians.

While there is certainly evidence for the effects of experience on the musician's brain, additional studies, e.g. investigating the time course of brain development in musicians and non-musicians, need to be conducted (e.g. Schlaug et al., 2003). The forthcoming sections will present and discuss studies assessing functional measures of plasticity.

2.3 Functional plasticity in the adult brain

Plasticity is the brain's lifelong ability to reorganize neural pathways based on new experiences. As animals and humans learn, they acquire new knowledge and skills through instruction or experience. In order to learn or memorize a fact or skill, persistent functional changes must occur in the brain in order to represent the new knowledge.

Merzenich and colleagues conducted the first studies that assessed functional plasticity in animals. Experience-dependent modifications of cortical maps and receptive fields were found in numerous studies. Some of their research studies were based on the hypothesis that temporally correlated afferent input activity plays a lifelong role in the establishment and modification of receptive fields and representational topographies in primary cortices of adult monkeys. In 1984, Merzenich and colleagues surgically amputated several fingers of several adult

monkey hands and found a change of the somatosensory map following the digit amputation in adult monkeys (Merzenich et al., 1984). The representation of the remaining digits increased and expanded to locations within the former territories of the amputated digits. In follow-up studies they surgically connected the skin of digits 3 and 4 in several monkeys in order to create an artificial syndactylyl (Allard et al., 1991). After several months, the cortical maps of the finger representation were highly modified, and surgically connected fingers no longer exhibited a discontinuity between the cortical maps of each finger. Thus, the representational topography of the joined fingers was similar to that of any remaining normal finger. The results suggest that cortical maps can be altered in detail even in adult monkeys by modifying the afferent input. Similar research findings were revealed for other domains, e.g. the primary auditory cortex, and will be further discussed in section 2.3.1.

The utilization of noninvasive PET/fMRI neuroimaging and EEG/MEG brain mapping of cerebral activation during conscious tasks since the early 1990s has inspired the investigation of functional plasticity in the human brain. One of the first studies to assess experience-dependent plasticity in the human brain was conducted by Karni et al. (1995). They demonstrated functional MRI evidence for adult motor cortex plasticity during motor skill learning. Following training on a complex motor task (rapid sequences of finger movements), subjects showed improvement in speed and accuracy. FMRI scans were obtained prior to during and after the training. After a short period of time, repeating the sequence resulted in a smaller area of activation, which the authors interpreted as habituation. Nevertheless, after four weeks of training, the extent of cortex activated by the practiced sequence enlarged and the revealed changes lasted for several months. These results after a one month training period suggest an experience-dependent reorganization of the human primary motor cortex. Several other studies in the motor domain support this finding (Schlaug et al., 1994; Jenkins et al., 1994; Pascual-Leone et al., 1995).

In addition the aforementioned experience-dependent plasticity, there is functional plasticity in response to sensory loss. Several studies showed that cortical areas normally reserved for one particular sensory modality might be activated by other sensory modalities following sensory loss in the particular domain. Sadato et al. (1996) revealed activation of the primary and secondary visual areas during a tactile task in early blind subjects, whereas deactivation of the visual areas was seen in sighted controls. These results suggest that the visual areas in early blind subjects

might subserve nonvisual functions, thereby indicating functional plasticity in respond to the lack of sensory input.

Others have found that the processing and localization of sounds in central auditory space is essentially the same in blind and sighted subjects. However, sound localization and the representation of auditory periphery is enhanced after congenital blindness (Roder et al., 1999). There might be a greater reliance on the auditory periphery by the blind for detecting potentially important events. This theory is supported by a series of studies by Neville & Lawson (1987a,b) and Bavelier et al. (2000) investigating cross-modal plasticity in congenitally deaf subjects. The authors investigated how deaf people process visual information. Their results are consistent with the results of Roder et al. (1999). Although there are not any differences between deaf and hearing subjects in some aspects of visual processing, such as the processing of central vision as well as color and form information, the perception of motion, especially in the far visual periphery is superior in the congenitally deaf subjects. As revealed for the blind subjects, the processing demands of a deaf person might strongly influence which aspects of visual processing might be modified. In order to identify motion in their periphery, hearing people rely on their audition. Because deaf subjects are not able to use this information, visual motion processing is enhanced in the deaf, indicating use-dependent cross-modal plasticity in both the deaf and the blind (for a review see Neville & Bavelier, 2002 and Bavelier & Neville, 2002).

In addition to the studies mentioned above, there is a growing body of literature assessing functional plasticity following lesions and training in various domains and populations, such as strokes (e.g. Zemke et al., 2003; Dobkin, 2003), dyslexia (e.g. Temple et al., 2003b), and language acquisition (e.g. Callan et al., 2003). The following sections 2.3.1 and 2.3.1 will provide an overview regarding functional plasticity in the auditory cortex and the influence of musicianship on functional brain changes.

2.3.1 Experience-dependent functional plasticity in the auditory cortex

Several experiments conducted in the motor and somatosensory domains (see above) have documented that cortical representations are continually shaped by experience. In Chapter 1, the structural and functional anatomy of the auditory cortex has been described in detail, and studies assessing functional plasticity in the auditory cortex will be discussed in the following section. While the anatomy and structure of

brainstem structures are relatively well preserved across species, the structure of neocortex, such as the auditory cortex, varies substantially across primates. It even shows wide diversity across primate species. This makes it very difficult to infer relationships between responses found in animal studies and the expected functional properties in humans.

While a significant amount of information has been gathered on cortical responses in cats, bats, owls and guinea pigs (Diamond et al., 1986; Edeline & Weinberger, 1993; Robertson & Irvine, 1989), this section will focus on training–induced functional plasticity in monkeys and humans in order to remain focused on the auditory system in primates.

In 1993, Recanzone and colleagues revealed plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys (see Figure 3). They successfully trained monkeys for several weeks to discriminate small differences in the frequency of sequentially presented tones. Several parameters, such as cortical representation, sharpness of tuning and latency of the response, were increased for the relevant frequencies in response to the training. However, only the cortical area of frequency representation correlated with behavioral performance. These results suggest a performance related modification of the primary auditory cortex in response to attended auditory stimuli in the monkey. However, it remains unclear whether these results can be generalized to the human auditory cortex.

Although many studies have investigated functional plasticity in the motor and visual domain in humans, functional plasticity in the human auditory cortex has not been well explored. Cansino & Williamson (1997) have conducted a similar experiment in humans as that conducted by Recanzone et al. (1993) in owl monkeys. Auditory evoked neuromagnetic fields of auditory regions were recorded while subjects performed a frequency discrimination task. The authors found evidence for cortical plasticity in one subject following a 200 hr training period, which showed a decrease of the relative magnetic field amplitude in auditory regions with improved discrimination. Furthermore, a difference in the spatial pattern of the magnetic field was revealed between correct and incorrect responses.

Another study (Menning et al., 2000) found an increase in amplitude in the slow auditory evoked and mismatch field (MMF) in response to a sequence of pure tones (1000 Hz) and deviant tones (oddball procedure) during a three week frequency

discrimination training period. Subjects had to detect deviants that differed from the standard tone by progressively smaller frequency distances. The effect could be observed after only one week and persisted until the end of the training. However, the responses decreased three weeks after the end of the training period, nearly reaching baseline level.

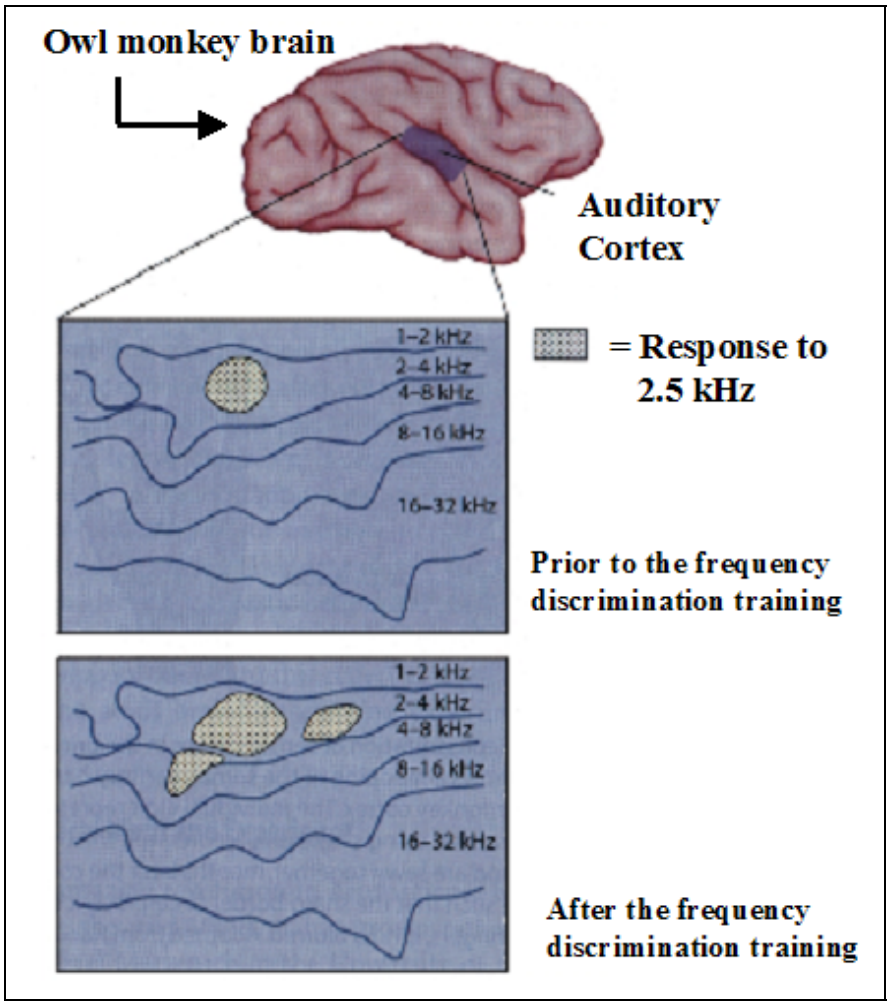

Figure 3: Results in the frequency representation of 2.5 kHz following a frequency discrimination training in the adult owl monkey (Recanzone et al. 1993).
(Figure modified from Gazzangia et al. 1996)

Using functional magnetic resonance imaging (fMRI), Jancke et al. (2001) revealed performance related plasticity in auditory areas. Subjects underwent one week of frequency discrimination training (oddball procedure) and were scanned prior to and after the training. Hemodynamic responses in the auditory cortex comprising the

planum temporale, planum polare and the sulcus temporalis superior significantly decreased following the training in only those subjects that improved during the training. Stimuli accompanied by the strongest performance gain during the training showed the strongest activation changes. There was no difference with respect to the hemodynamic responses in the auditory cortex for those subjects, who were trained but showed no improvement. Likewise, a control group that did not undergo any training showed no changes.

Overall, the few auditory learning studies conducted so far have not shown a cohesive picture in terms of the brain regions modulated in response to nonverbal auditory training and the direction of the modulation. Some studies revealed activity increases whereas some showed decreases after the training. Moreover, there seems to be a strong relationship between performance improvement and cortical changes.
Furthermore, the aforementioned studies showed alterations of cortical responses following a short-term or long-term auditory discrimination training period. But functional plasticity can be observed even sooner than that. Pantev et al. (1999) revealed short-term or even rapid plasticity in the human auditory cortex using magnetoencephalographic measurements. They assessed the effect of removing a specific frequency from the subjects' acoustic environment. Subjects in this study listened to music, which lacked the frequency band centered around 1000 Hz. After three hours of music exposure, the neural representation of a 1000 Hz stimulus was significantly reduced in comparison to a control tone of 500 Hz. This effect was reversible, could not be longer revealed after a 24 hour time period and can be explained by rapid plastic changes in human auditory regions.

In addition to studies assessing functional plasticity following simply auditory tasks such as frequency discrimination, there is some evidence for plastic changes following more complex stimuli, such as speech in normal subjects, nonnative speakers and dyslexics (Callan et al., 2003; Golestani et al., 2002; Hayes et al., 2003; Menning et al., 2002; Tremblay et al., 1998, 2001, 2002; Kraus et al., 1998; Temple et al., 2003b; Kujala et al., 2003).

The auditory cortex is crucial for human communication and the above-described studies provide evidence for cortical changes in respond to non-verbal and verbal training. Like language, music is processed by a network, which involves the auditory cortices. Consequently, musical training might trigger functional similar to those observed for simple auditory task and complex auditory task, such as speech. In

the following section, a brief overview regarding functional differences in auditory processing between musicians and non-musicians will be provided.

2.3.2 The influence of musicianship on auditory processing

Structural differences occurring between musicians and non-musicians were discussed in section 2.2.1. However, there is also a growing body of literature assessing functional change in response to musical training between these two groups, which this section will provide a brief overview of.

Several studies have revealed functional differences between musicians and non-musicians in perisylvian brain regions with various perceptual tasks, including listening to music or performing pitch, harmony, melody or rhythm tasks, particularly for musicians who commenced practice at an early age. Besson et al. (1994), for instance, used EEG and found a musicianship effect when subjects listened to musical phrases that ended either in a congruous or a harmonically, melodically or rhythmically incongruous note. Brain waves differed (e.g. in temporal aspects) between the two groups as a function of the subject's familiarity with the melodies and the type of incongruities. This study suggests differences in auditory processing (in particular temporal auditory processing) between musicians and non-musicians. Further evidence for differences in auditory temporal processing was provided by e.g. Russeler et al. (2001).

Not only have studies revealed changes in temporal auditory processing between the two groups, but two studies have also revealed superior auditory spatial processing in orchestra conductors compared to pianists and non-musicians (Munte et al., 2001; Nager et al., 2003). These results corroborate the findings discussed in section 2.3.1, which have documented not only that cortical representations are continually shaped by experience but also and this effect can be seen in several domains. For instance, in a study by Pantev et al. (1998), which assessed auditory cortical representation in professional musicians with MEG, musicians showed increased dipole moments for piano tones compared to non-musicians. However, pure tones of the similar fundamental frequency showed no difference. The authors interpret their results with use-dependent functional reorganization in response to long-term training of musical skills, particularly training of the piano timbre. Several other studies have also revealed timbre-specific cortical changes, e.g. in violin and trumpet players (Pantev et al., 2001; Crummer et al., 1994).

Most of these studies, which indicate that musicians might process music in a different way, show a lateralization effect, indicating a greater hemispheric activation with increased musical sophistication on the left side than on the right. This is consistent with previous studies, which showed left more than right hemispheric processing depending on musical expertise (Kimura, 1964; Johnson et al., 1977; Bever & Chiarello, 1974; Mazziotta et al., 1982; Hassler, 1990; Messerli et al., 1995; Evers et. al., 1999; Ohnishi et al., 2001).

It appears that musical expertise also influences pre-attentive auditory processing. Using a mismatch negativity paradigm (MMN) Koelsch et al. (1999) found superior pre-attentive auditory processing in musicians compared to non-musicians. In musicians, dissonant chords elicited an MMN under "attend" and "ignore" conditions. This was not the case, however, in non-musicians. Since effects of long-term experience on pre-attentive auditory processing have been reported for the language domain, the authors argued that sensory memory mechanism might be modulated on a general level by training.

As several studies for blind subjects have revealed (see above), the processing demands of a person (e.g. conductor or a pianist) appear to influence which aspects of auditory processing might be modified in the brain. Nevertheless, it remains ambiguous whether these effects are a result of long-term musical training or hereditary traits that influence the decision to embark musical training (see also discussion in section 2.2 on structural plasticity).

Furthermore, research has also been conducted in attempt to assess functional differences between musicians and non-musicians in domains other than auditory, such as motor (Jancke et al., 1997, 2000b; Hund-Georgiadis & Cramon, 1999; Krings et al., 2000; Pascual-Leone, 2001; Bangert et al., 2001, 2003; Haueisen & Knosche, 2001; Schlaug et al., 2001) or somatosensory, (e.g. Elbert et al, 1995; Byl et al., 2000). There is also a growing body of literature evaluating functional differences within the group of musicians, particularly musicians with absolute pitch and those without absolute pitch (e.g. Zatorre et al., 1998, 2003; Schulze, 2003; Hirata et al., 1999; Onishi et al., 2001; Crummer et al., 1994; Hirose et al., 2002, 2003, Schlaug, 2001).

2.4. The influence of sleep on synaptic plasticity and learning

There is a wide body of research at behavioral, physiological, cellular and molecular levels, indicating the important role of sleep in the plastic cerebral changes that underlie learning and memory, particularly in the consolidation of new memory traces.

The influence of sleep on learning can be demonstrated by two distinct types of experiments. First, several studies, which assessed the relationship between learning, memory, and sleep by combining behavioral, neuroimaging and somnographic experimental designs (neurocognitive studies), examined the correlation of improvement of memory, procedural and perceptual tasks. Sleep variables, such as sleep duration, quality or deprivation and specific sleep stages, e.g. sleep augmentation, were investigated. The second category assessing the influence of sleep on learning assesses the neurochemical and neurophysiological changes of sleep, including sleep and RNS/DNA synthesis, sleep and gene expression, and sleep and protein synthesis. Some studies synthesize this two research directions.

Two important findings can be derived from the neurocognitive studies conducted so far. First, sleep amounts in general - and REM sleep in particular – is reported to increase following a learning period (e.g. Walker et al., 2002). Furthermore, sleep appears to have a strong influence on learning in various domains, particularly for procedural tasks (Karni et al., 1994; Stickgold et al., 2000a,b; Walker et al., 2002, 2003; Gais et al., 2000; Peigneux et al., 2001). Most of these studies have revealed a delayed task improvement only across a night of sleep and not across a similar long time period of wakefulness, regardless of which came first in the experimental design. Moreover, sleep deprivation following a learning task seems to impair task acquisition (e.g. Block et al., 1981; Smith 1985, 1995; Siegel, 2001; Fishbein & Gutwein, 1981; Horne, 2000).

Generally, sleep enhances and sleep loss diminishes processes such as learning and memory that entail synaptic plasticity.

Neurochemical studies have revealed that the synthesis of genes and proteins required for synaptic plasticity actually takes place during sleep. Furthermore, sleep and sleep loss appear to modify synaptic strength and patterns of synaptic connectivity on both the cellular level and molecular level, e.g. influence of sleep on LTP and LTD or synchronization of neuronal activity in thalamocortical and

hippocampal-neocortical networks in nonREM and REM sleep (for a review see Benington & Frank, 2003).

Overall, these studies provide evidence that sleep facilitates learning, memory and synaptic plasticity (for a review see Benington & Frank, 2003, Maquet et al., 2000, 2001, 2003; Stickgold et al., 2002) and highlights the need to consider the influence of sleep on learning in future studies assessing training induced plasticity.

3. Functional magnetic resonance imaging (fMRI)

Functional brain mapping with magnetic imaging (MRI) is a rapidly growing field that has emerged only recently. The goal of fMRI is to map the spatiotemporal distribution of neuronal activity during specific cognitive states. By monitoring hemodynamic changes, fMRI indirectly localizes brain functions. Most techniques use the blood oxygenation level dependent (BOLD) contrast in order to investigate what areas of the brain are responsible for specific e.g. cognitive and perceptual processing. The BOLD contrast is based on the differing magnetic properties of oxygenated (diamagnetic) and deoxygenated (paramagnetic) blood. These differences in magnetic susceptibility lead to small, but detectable changes in susceptibility-weighted MR image intensity. Detection of activation related signal changes could be complicated by various factors, such as relatively low image signal-to-noise-ratio (SNR), head movement and undesired physiological sources of variability.
The subsequent section of this body of research will discuss strategies for overcoming these problems, the design and functionality of an MRI scanner, and commonly used statistical methods for analyzing the fMRI data.

3.1 Functionality of an MRI scanner

3.1.1 Magnet components and larmor frequency

Magnetic resonance imaging (MRI) emerged from a physical phenomenon known as Nuclear Magnetic Resonance (NMR), which deals with the magnetic properties of the nucleus of atoms. The here described technique deals in particular with the nucleus of a hydrogen atom (a single proton), because water is the biggest source of protons in the body, followed by fat. Two of the basic properties of a single proton are a positive electric charge and a spin.

A moving electric charge produces a magnetic field. The faster a proton moves the larger is the magnetic field it produces. Although a proton does not have a large electric charge, it spins extremely fast and consequently produces a small, detectable, magnetic field (see Figure 4). The direction that the protons point in is randomly distributed because some of these protons align with a large external field (Bø)(parallel) and some actually align against it (antiparallel, see Figure 5). They obey the Botzmann statistics and therefore a slight majority aligns with the magnetic field, which results in a lower energy state (alignment with the field leads to a lower

energy state). The total magnetic field of the excess protons is called Mø (net magnetization or magnetization vector). At 1.5 Tesla, for only 9 more protons are aligned with the field than against the field for every 2 million protons.

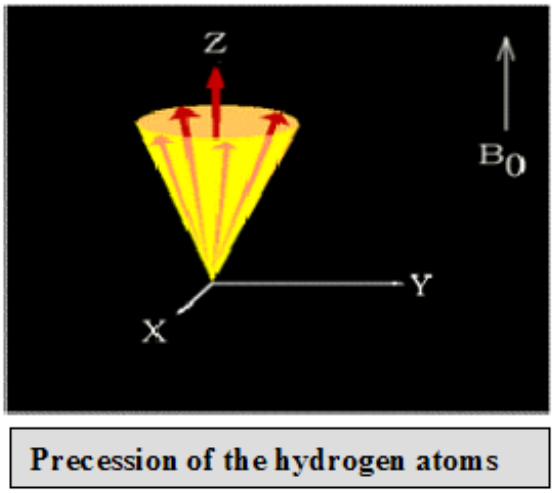

Figure 4: Precession of the hydrogen atoms
(modified from http//: www.erads.com)

The high resolution in MRI is thus not explained by the high level of energy involved but rather by the amount of hydrogen protons in water and fat (6 million protons in one voxel of water). The protons (spins) that align with or against Bø are also slightly tilted. However, they are precessing at a speed of approximately 2 million times per second.

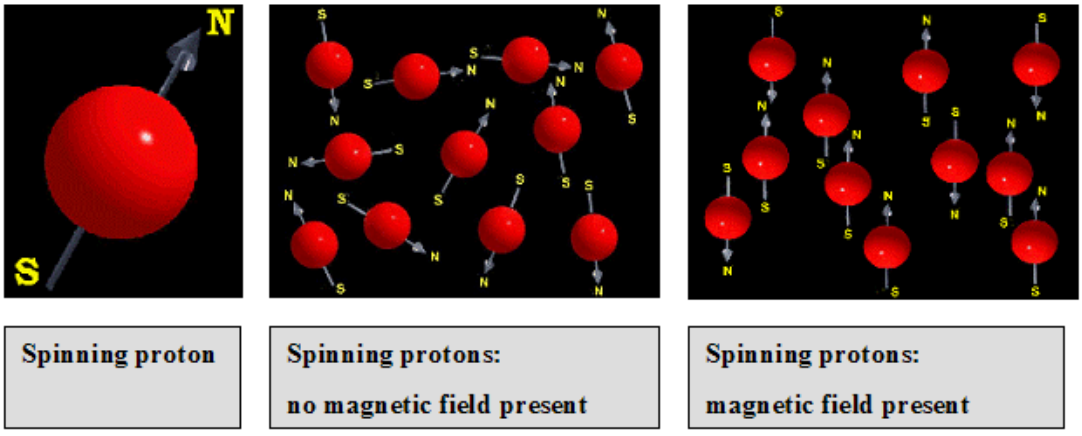

Figure 5: Spinning protons and their alignments in the magnetic field
(modified from http//: www.erads.com)

The spinning protons precess about the axis of the external field Bo and the frequency of the precession is directly proportional of the strength of the magnetic field (see Figure 5). This is defined by the larmor equation:

$\omega ø = \gamma B_0$
ωø = resonance frequency (or larmor precessional)
γ = gyromagnetic ratio (a constant unique to every atom)
Bø = main magnetic field, measured in Tesla

When averaged over a short period of time, the position of the spins results in perfect alignment either with or against the magnetic field.

3.1.2 Signal detection

If an electromagnetic radio frequency (RF) pulse is applied at the larmor frequency, then the protons are able to absorb that energy. This means that more proton flip from 'aligned with' to 'aligned against' B_0, thus gaining a higher energy state and hence changing the net magnetization. The magnetization vector, Mø, spirals down towards the XY plane (or the negative Z axis, see Figure 6). This can also be represented by a stationary X'Y' coordinate system, which represents a rotating frame (transverse plane). The magnetization vector, (Mø) can be understood as tipping smoothly down towards the Y' axis here (see Figure 6). This tip angle α is a function of the strength and duration of the applied RF pulse. A short and weak RF pulse can cause a 10 degrees flip angle and a longer and/or stronger pulse can produce a 90 degrees angle.

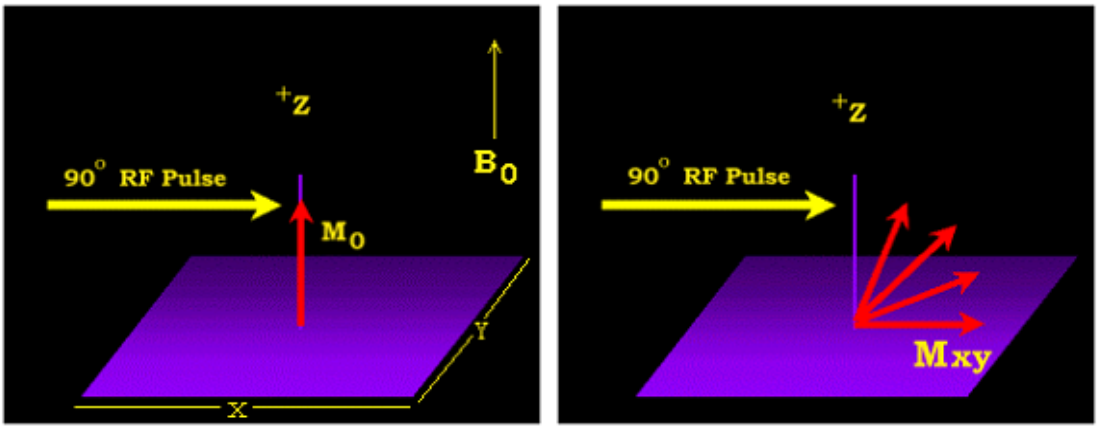

Figure 6: Signal detection (http//: www.erads.com)

3.1.3 Relaxation times

The next step is to turn off the electromagnetic radio frequency pulse (RF), which triggers three effects simultaneously (see Figure 7). First, the absorbed RF energy is retransmitted at the larmor frequency, thereby producing the NMR signal. The mechanism behind that is that a vector rotating in the transverse plane releases electromagnetic radiation (radio waves). As soon as the magnetization vector (Mz) has been tilted away from the Z-axis, Mz continues to precess around the external field at the larmor frequency. Since a rotating magnetic field produces electromagnetic radiation and ωø is in the radio frequency portion of the electromagnetic spectrum, the rotating vector is said to give off RF waves. The absorbed RF energy is being retransmitted and produces the NMR signal.

Second, the excited spins begin to return to the original Mz orientation (relaxation). The RF emission is the result of the magnetization recovering back to Mø. However, not all of the transmitted energy is detectable as an RF pulse. Some of the energy heats up the surrounding tissue (lattice). This spin lattice interaction is the result of the excited system returning to thermal equilibrium. The process by which the Mo goes back to its original value (also called recovery of longitudinal Bø magnetization) is called T1 relaxation:

In summary, T1 relaxation, which is used in anatomical images, is the process whereby energy absorbed by the excited protons or spins is released back into the surrounding lattice, reestablishing thermal equilibrium. The time that it takes for the system to return to thermal equilibrium, or Mz grows to Mo is described mathematically by an exponential curve. This recovery rate is characterized by the time constant T1, which is unique to every tissue (emitted by water protons between different tissues). The uniqueness of Mz recovery rates enables MRI to differentiate between various types of tissue. In general, the higher the water content of a tissue is, the longer the T1 relaxation is. The gray-white contrast is possible in MRI because these two types of tissues differ with regard to T1.

The third effect that results from turning of the radio frequency pulse (RF) is the dephasing of the excited protons which is called T2 and T2* relaxation.

Because protons precess (spin) at different rates, they quickly get out of phase relative to the spins at the center of the magnet, which results in NMR signal decay. How quickly a proton precesses depends on the interacting magnetic field. An isolated proton is only affected by Bø. As random motion can cause protons to precess

together, their magnetic fields begin to interact. If two interacting spins move further apart, their fields will no longer interact causing them to return to their original frequencies, but at a different phase. This type of interaction is called spin-spin interaction. Temporary, random interactions result in a cumulative loss of phase across the excited spins causing an overall loss of signal. This interaction is random and the loss of phase is permanent. In summary, the temporary and random interaction between two spins that causes a cumulative loss in phase resulting in an overall loss of signal is called transverse relaxation (also spin or T2 relaxation; T2 decay).

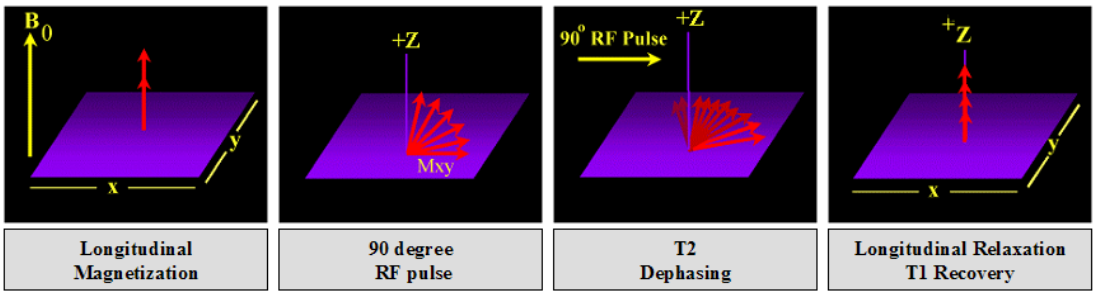

Figure 7: Longitudinal Relaxation (modified from http//: www.erads.com)

Unlike T1 values, T2 values are not related to field strength. Pure T2 decay is a function of completely random interactions between spins. The assumption is that the main external field Bø is absolutely homogeneous, but many factors can lead to imperfections in the homogeneity of a magnetic field. The sum total of all these random and systematic effects is called T2*. In summary, T2 relaxation results from random causes while T2* results from a combination of both random and systematic causes. The oxygenation state of the blood is strongly influenced by the microvascular MR signal on T2 and T2* weighted images. As described earlier, the rate of loss of proton spin phase coherence is a measure of T2 and local magnetic field homogeneity (T2*). This can be modulated by the presence of intravoxel deoxyhemoglobin. Recent data shows that the observed T2* depends upon the presence of blood deoxygenation and that deoxygenated hemoglobin is a “blood oxygenation level dependent”, or BOLD, effect that can be observed by noninvasive MR imaging at high magnetic fields. The following section will describe this effect in detail.

3.2 The BOLD contrast in fMRI

A variety of tissue contrast mechanisms, e.g. proton density or T1 and T2 relaxation rates lead to differences in image intensity observed in MR images. One tissue contrast, the BOLD contrast, has functional sensitivity in MR imaging and is produced via hemodynamic responses.

The microvascular MR signal on T2 and T2* weighted images, is strongly influenced by the oxygenation state of the blood. When a region of the brain is activated, the blood flow to this region increases in order to compensate for the used oxygen. In fact, the blood flow increases so much, that the venous and capillary concentration of deoxyhemoglobin actually decreases. This is significant for the relation between NMR signal change and neuronal activity, because deoxyhemoglobin is paramagnetic, affects the local observed T2* and therefore causes fluctuations in the magnetic susceptibility (the intensity of magnetization of a body placed in a uniform magnetic field of unit strength) These inhomogenities (disturbance of the local magnetic field B0) cause the signal to decay faster and the NMR decreases (intravoxel T2 and T2* are shorter) as a result of a large observed magnetic susceptibility effect.

By increasing the flow of oxygenated blood or reducing oxygen extraction from a region in the brain an increase in local, intravoxel T2* occurs, causing an increase in MR signal (image intensity) for active regions of the brain (intravoxel T2* becomes longer). This can be observed from intensities measured from T2*-weighted MR images or by simply subtracting images acquired at rest from those acquired during the task. Gradient echoes are particularly sensitive to magnetic field inhomogeniety and are consequently frequently used in fMRI.

Nevertheless, in order to design an experimental task for the fMRI environment one should know, that the hemodynamic response occurs with a 3-6 sec. delay depending on the brain region and/or the nature on the task (see e.g. Kwong et al., 1992; Belin et al., 1999). The software programs that are commonly used to analyze fMRI account for this. In short, a local increase in metabolic rate triggers the increased delivery of oxygenated blood to the activated brain region about 6 seconds after the neuronal response. Such a change in hemodynamics produces small alterations in T2*, which can be visualized as a change in MR image intensity. Thus,

the local T2*, which is critical in the fMRI contrast, is determined by the ratio of deoxygenated to oxygenated hemoglobin in blood within a voxel.

3.3 Auditory stimulation and fMRI

One major disadvantage of MRI and especially fMRI is the beeping background noise, which can e.g. interfere with auditory processing (Talavage et al., 1998; Bandettini et al., 1998; Ulmer et al., 1998; Belin et al., 1999). This noise is results from the mechanical oscillation of the gradient coils placed in a magnetic field (e.g. Hedeen et al., 1997). Through wires in the gradient coil, currents create the gradients. The currents are switched back and forth rapidly, and the Lorentz force on the wires causes the coil assembly to vibrate rapidly (Mansfield et al., 1998). Echo Planar Imaging (EPI) (Mansfield & Pykett, 1978) is currently the pulse sequence, which is most widely used to acquire neural correlates of brain functions. EPI typically generates high-frequency noise, which peaks around 1000 Hz, particular when used at high image resolution. Typically, the amplitude of the acoustic noise varies from approximately 90 to 150 dB and is dependent upon various parameters, such as characteristics of the scanner materials, the number of slices acquired, the effective repetition time (TR) or the field of view (FOV). This could be specifically problematic in studies of the auditory system, imposing restrictions on the design of the activation paradigm (Belin et al., 1999; Eden et al., 1999).

Several methods of addressing this problem have been discussed in the literature. This includes modifications of the hardware components of the scanner (e.g. Mansfield et al., 2000, 2001; Ravicz et al., 2000) as well as alterations of the software (e.g. Hennel et al., 1999; Oesterle et al., 2001; Zwart et al., 2002) used for the experiments. A number of studies have also suggested modifications of the experimental design (see section 3.3.1 and Talavage et al., 1998; Hall 1999, 2000; Edmister, 1999; Yang et al., 2000) or approaches that focus specifically on reducing the acoustic noise by e.g. using sound dampening devices such as earplugs or active sound cancellation systems (McJury 1995, McJury et al., 1997; Cremillieuz et al., 1997; Goldman et al., 1989). For a review of the current strategies and future prospects of dealing with the acoustic noise in fMRI see Amaro et al. (2002).

One of the modifications of the experimental design, referred to as the “sparse temporal sampling” method, will be further discussed in more detail.

3.3.1 The "sparse temporal sampling" method

As described earlier, the noise created by the gradient coil switches poses a challenge for performing auditory tasks in the MR environment. This "scanner noise" can (1) interfere with the auditory stimulation (Bandettini et al., 1998; Shah et al., 1999, 2000; Hall et al., 2000), (2) result in masking of the auditory cortical response depending on the frequency of the MR acquisition, (3) lead to activation of the auditory cortex itself depending on the effective repetition time (TR) for MR acquisitions (Bandettini et al., 1998; Scheich et al., 1997; Ulmer et al., 1998), and (4) causes discrepancies in the attentional demands if frequency and intensity of the MR scanner noise differ between studies.

A few imaging designs have been proposed to overcome these interferences (Edmister et al., 1999; Hall et al., 1999, 2000) using the "sparse temporal sampling" method. In this method, single volumes of brain images are acquired at the end of the stimulus and baseline conditions. To optimize detection of the activation without sampling the whole hemodynamic response function, images should be taken near to the maxima and/or minima of the hemodynamic response during the experimental cycle. Hall et al. (1999) compared continuous scanning with a sparse temporal sampling method, using an effective repetition time (TR) of 14s and revealed a greater MR signal change for acquisitions with a long TR. In addition, it was found that recording scanner noise and playing it back to the subject could lead to a signal change of up to 1.5% in primary and secondary auditory cortex. Hall et al. (1999, 2000) showed further that the activation peaked 4-5s after stimulus onset and decayed after an additional 5-8s.

Others have shown a decrease in the spatial spread and lower z-scores of the activated auditory regions depending on the duration of the MR scanner noise (Shah et al., 1999). Belin et al. (1999) used an effective TR of 10s and varied the delay between a short auditory stimulus and the MR acquisition. Primary auditory cortex showed a maximum response about 3s after stimulus onset and lasted 3s before it decayed. Overall, these studies showed, that sparse imaging is advantageous in auditory experiments since it avoids the four aforementioned problems of auditory stimulation in the presence of scanner background noise.

3.4 Methods of analysis

3.4.1 Preprocessing in fMRI

The purpose of preprocesing in fMRI is to correct for non-task related variability in experimental data. These approaches are usually performed without any consideration for the experimental design and therefore are called preprocesssing. The preprocessing steps seek to remove, rather than model data variability. One important term in fMRI analysis language is the *signal-to-noise-ratio* (SNR), which is the quotient between task-related variability and non-task-related variability. The goal of the preprocessing is to remove as much non-task-related variability as possible in order to obtain a high SNR value. The sensitivity of an fMRI analysis is determined by the amount of residual noise (non-task related variability) in the image series.

The following sections describe four basic steps of preprocessing (although the number of steps depends on the applied experimental design). A number of tools and software programs are available for preprocessing and analysis, such as SPM (http://www.fil.ion.ucl.ac.uk/spm), Brain Voyager (http://www.brainvoyager.com), VoxBo (http://www.voxbo.org), AFNI (http://afni.nimh.nih.gov/afni/). For a detailed description of preprocessing using the software program SPM see Friston et al., 1997 (in Frackowiak et al., 1997; see Figure 8).

3.4.1.1. Motion correction:

Motion correction corrects the data for movements of the head; it controls for motion-related variance. Small movements of approximately 1mm occur (Turner et al., 1997; Franckowiak et al., 1997) even if the subject's head is fixated and the subject tries explicitly not to move. In addition, there are movements related to physiological factors, such as cardiac and pulmonary parameters. These movements can e.g. alter the "spin history" as a result to the change of position relative to the gradients of the scanner. Moreover, often it is impossible to eliminate the voxels in the activation pattern that are activated by an artifact that has arisen as a result of motion. The functional volumes are aligned in space by rigid-body transformations. The software program SPM employs a least-squares approach and a 6 parameter (rigid body) spatial translation (Friston et al. 1996). In this approach, the first image in a time-series serves as a reference scan against which all subsequent scans are aligned. Motion correction has several limitations, including artifact-related limitations, which can

result in a loss of data around the edges of the image volume. Distortions in fMRI images can also pose a problem because distortions may be dependent upon position in field, rather than position in the head. Therefore the rigid body model does not model these types of distortions.

3.4.1.2 Coregistration:

In order to coregister the anatomical and functional images, the software program in SPM requires three steps. First, it uses simultaneous affine registrations between each image and a template image of the same modality (functional or anatomical). Next, SPM separates the images into white and gray matter (segmentation). Finally, white and gray matter partitions acquired during step two are simultaneously registered via the sum of squared difference.

The fMRI literature is ambiguous as to whether functional and anatomical images should be coregistered. Coregistration may improve normalization and allow activation on anatomical images to be displayed. It also permits comparison across modalities in an individual's brain. Nevertheless, possible disadvantages of coregistration exist. For example, coregistration may severely distort functional data and may dimish correspondence between functional and anatomical images.

3.4.1.3 Normalization:

This preprocessing step spatially (stereotactically) normalizes images into a standardized space, which is defined by some ideal model or template image. It can thus be described as an intersubject averaging method. The software program SPM conforms the Montreal Neurological Institute (MNI) space (a combination of many MRI scans on normal controls; all right-handed subjects) and approximates that of the space described in Talaraich and Tournoux's atlas (1988). Generally, these algorithms work by minimizing the sum of squares differences between the acquired images and the template (for automated algorithms see e.g. Ashburner & Friston, 1997, 1999). One major advantage of the normalization is that it allows the generalization of results to a larger population, thereby enabling averaging across subjects and improving comparisons with other studies. Normalization also provides coordinate space to report the results. One disadvantage of normalization can be cited in its potential to reduce the spatial resolution resulting from differences in interindividual brain organization and thus may reduce the activation strength by averaging subjects.

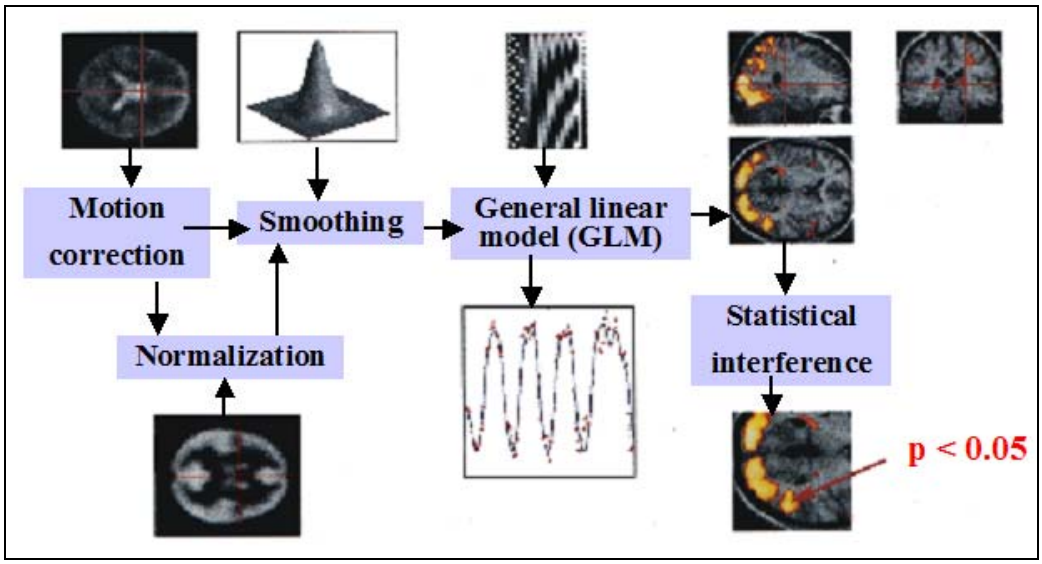

Figure 8: Analysis steps for fMRI data (modified from Franckowiak et al. 1997)

3.4.1.4 *Spatial Smoothing:*

Spatial smoothing convolves images with an isotropic Gaussian kernel [defined by its full width at half maximum (FWHM)] to potentially increase SNR, to compensate for residual between-subject variability after normalization, and to approximate a random field for statistical purposes (see multiple comparisons below). Issues such as reduced spatial resolution, which relate to smoothing, are discussed in detail in Friston et al., 2000.

3.4.2 Statistical analysis of fMRI data

Several methods based on the General Linear Model (GLM) can be employed to assess brain activity in fMRI studies. The basic concept of the GLM is, that it treats the data as a linear combination of model functions plus noise. Typically, these methods result in a statistical parametric map. In order to obtain these parametric maps, each of these methods entails comparable successive steps.

First, the response (signal) will be modeled at each voxel in the brain by a GLM. Subsequently, a hypothesis regarding the model's parameters will be tested. The observed statistic map will then be represented at a given level (threshold) according to the point of distribution of the statistics (uncorrected level) or the field distribution of the statistics (corrected levels for local maxima). A correction to the significance of the t-statistics is suggested, which account for the multiple

comparisons in the image (see multiple comparisons below). Afterwards, the statistical parametric map can be visualized showing e.g. the t-value for each single voxel with a corresponding color on an image of the brain. Overall, these methods are voxel-by-voxel hypothesis testing approaches, which reliably identify regions showing a significant effect of interest.

The GLM model used can refer to a single subject, one group of subjects or multiple groups of subjects, which can represent different subjects (e.g. musicians and non-musicians) or the same subjects (e.g. prior to training versus after training of an auditory task). The modeling part is univariate and thus separated for each voxel and usually each subject as well. For a simple t-test, the GLM is also utilized in order to account for covariates as well as temporal autocorrelation. Multi-subject fMRI experiments can also be performed using a GLM framework with different forms depending on the approach taken, e.g. fixed or random subject analysis. Fixed-effects model uses data from all subjects to construct a statistical test. This method allows interference to the analyzed subject sample. A random-effects model accounts for inter-subject variance in analyses and permits interference to population from which subjects are drawn, which is essential for group comparisons.

3.4.2.1 Multiple comparisons:

Most statistics packages for functional imaging data create statistical parametric maps (see above), which have a value for a certain statistics (e.g. t-statistics) at each voxel in the brain. This results from the statistical test performed voxel-wise between states (experimental tasks) within one subject or over a number of subjects.

One major problem arises, however, if more than one test is made, the collective alpha value is greater than the single test alpha (overall Type I error increases).

One option is to adjust the alpha value of the individual tests in order to maintain an overall alpha value at an acceptable level (controls overall for Type I error; known as Bonferroni correction). However, conventional multiple comparison methods (e.g. Bonferroni) may overcompensate resulting in very strict significance values for even small data sets.

This problem might be explained by the fact that this approach is not appropriate for correlated data. If data set contains correlated data points, then the effective number of statistical tests may be greatly reduced and most fMRI data has significant correlations.

Several approaches are used in fMRI analysis software programs. Some of the primary examples include an approach using the random field theory (Worsley et al.1995, 1999, 2002), which provides false positive rate for fMRI data based upon the smoothness of the data, a randomization-based analysis across replications, and applying a small volume correction, e.g. a Region of interest (ROI) analysis (see also section 3.4.3). A ROI can only be used if an *a priori* hypothesis has been made.

3.4.3 Region of interest (ROI) analysis

Several software programs (MRIcro, BrainVoyager,) include the method of drawing and analyzing (e.g. time courses) a Region of Interest (ROI), which can complement a voxel based analysis. Each ROI can be considered a very large volume element (e.g. voxel). This method allows direct, unbiased measurement of activity in a predefined anatomical region, although, it assumes that functional divisions tend to follow anatomical divisions. Because it does not require correction for the number of comparisons, this hypothesis driven approach has more statistical power. Furthermore, a ROI is not smeared due to inter-subject averaging and improves the ability to identify topographic changes (e.g. motor mapping in the central sulcus). Nevertheless, it should only be used based on previous assessed, clear identified anatomical regions, which allow a directed hypothesis. Since functional ROIs result from statistical tests, they cannot be used to reduce the number of comparisons.

II. EMPIRICAL PART

4. General aims

Based on the review of the literature in chapters 1-3, the following general aims for this body of literature were developed:

General aim 1: *Development of an auditory task, which contains a perceptual and a memory component.*

General aim 2: *Modification of the sparse temporal sampling method in order to assess the time course of cerebral activity independent of scanner noise interference.*

General aim 3: *Assessment of training- induced functional brain changes in the auditory system using a pitch memory task.*

General aim 4: *Assessment of the influence of performance on functional brain patterns for the auditory domain.*

General aim 5: *Assessment of the role of musicianship in auditory processing (for the developed task)*

General aim 6: *Assessment of the role of gender in auditory processing (for the developed task)*

General aim 7: *Assessment of the role of sleep in auditory processing (for the developed task)*

5. Design of the pitch memory task

5.1 Criteria for the experimental task

In order to assess the general aims described in chapter 4, an experimental task had to be designed. The following citeria were used in the task design:

a) No ceiling and bottom effects

One of the specific aims of this body of research is the assessment of training induced changes in the brain's auditory domain. Therefore, it was decided that a task should exhibit a normal learning curve in normal subjects over the course of a one-week training period. Since possible functional changes will be correlated with performance and performance improvement, a ceiling and bottom effect should be avoided.

b) Initial performance above chance

The aim of the first empirical study is to assess the baseline for the designed auditory task. Additionally, the subjects' performance will be correlated with the functional anatomy in order to identify performance-related differences in the population.

c) *Musical versus nonmusical task*

In order to investigate possible functional differences between professional musicians and non-musicians, the task should employ a non-musical task. Therefore, pure sinus tones (tones without any timbre or harmonic information) will be used. A mixture of tones corresponding to the frequencies of semitones in the Western musical scale (based on A = 440 Hz), and tones that do not correspond to fundamental frequencies of the Western musical scale (e.g. microtones) will be used.

d) Perception versus higher cognitive functions

Previous studies assessing functional plasticity in the auditory domain in humans and animals used pure perceptual tasks (e.g. Recanzone et al., 1993; Menning et al., 2000; Cansino & Williamson, 1997; Jancke et al., 2001; for a review, see section 2.3). In order to assess auditory discrimination functions as well as higher order auditory cognitive functions (e.g. pitch memory), a memory component was added to the experimental task.

e) Required attention throughout the duration of the task

A further aim of this research was to assess the time course of activation during the experimental task prior to and following an intensive training period. Therefore, the location of target tones was varied (e.g. first tone had to be compared with last or second last tone and sequences were of two different lengths) requiring subjects to listen carefully to all tones in the experimental task while maintaining a constant attention level throughout the task.

f) Minimal verbal component

Since several studies have revealed similarities and differences between speech and a variety of nonverbal auditory tasks (e.g. Besson et al., 1998; Patel et al., 1998a,b; Tervaniemi et al., 1999, 2000; Schon et al., 2002; Koelsch et al., 2002), the task should be designed to involve minimal or no verbal component. If a verbal component is unavoidable, a control task that specifically avoids language-related activation in auditory and/or non-auditory areas must be designed.

Based on the aforementioned criteria, a pitch memory task was developed. Deutsch et al. (1974), designed a task, which required subjects to compare the pitches of two test tones, separated by a retention interval that contained eight interpolated tones.

In one condition, all of the distractor tones were taken from the same octave as the target tones. In a second condition, the distractor tones were drawn from one octave below, and, in a third condition, from one octave above. The amount of interference produced in each of these conditions varied depending on which octave the distractor tones were placed in. The largest performance decrease occurred when the distractor tones were taken from the same octave. The results indicate that the amount of interference produced by the distractor tones within the retention interval depends on the pitch relationship between the target and distractor tones.

In a study of Siegel et al. (1974), the authors employed a pitch memory task in order to assess whether the ability to perceive and process pitches categorically differed between subjects with absolute pitch and musicians without absolute pitch. Subjects were asked to listen to a series of pitches, and determine whether the first and the last ones were the same or different. The most likely strategy used to solve this task is to memorize the first pitch, ignore the intervening distractor tones, and compare the last

pitch to the first. Consequently, this task can be considered more of a pitch memory task than a pitch discrimination task. It would be better to require that subjects listened carefully to all of the tones regardless of whether they are target tones (the two to be compared) or distractor tones.

Zatorre et al. (1994) used a very similar task in a PET study. In this experiment, subjects listened to a melody and compared the first and last pitches. This condition was designed to investigate short-term pitch retention under varying pitch memory loads. When this pitch memory task was contrasted with a passive listening task, a right inferior frontal region became activated, indicating an involvement of frontal regions in auditory working memory. These results suggest that pitch comparisons are made via a neural network that includes the right prefrontal cortex.
Based on the aforementioned criteria, the pitch memory task by Siegel et al., 1974, Deutsch et al., 1974, and Zatorre et al., 1994, will be modified and used to investigate this study's general and specific aims (chapter 4).

5.2 The developed pitch memory task

During the pitch memory task, subjects will be instructed to listen to a sequence of either six or seven individual sine wave tones with a duration of 4.6s per sequence (Figure 9A). Each tone is 300msec long with an attack and decay rate of 50msec. A pause of 300msec separates each tone from the next. Target tones correspond to the frequencies of semitones of the Western musical scale (based on A= 440 Hz) and range in frequency from 330 (D#4) to 622 (D#5). Semitones within that range are used as target tones. The absolute frequency difference between the first and the last or second last tone lies between 41.17 Hz to 64.23 Hz in these trials in which the target and probe tones were different. There were five possible frequency differences in this range (diff1= 41.17Hz; diff2= 44.64Hz; diff3= 51.74; diff4= 56.12Hz and diff5= 64.23Hz). In each tone sequence, the frequency range from the lowest to the highest tone is not more than 108 Hz. Based on the interference results of the study of Deutsch et al. (1974), microtones are used only as distractor tones. No tone sequence has a frequency range from the lowest to the highest tone that exceeds 108 Hz. In the pitch memory task subjects will have to compare either the last or the second last tone (depending on the visual prompt "second last" or "very last") to the first tone and subjects will be asked to make a decision whether these tones were same or different

(Figure 9A). The total number of tones varies (6 or 7 tones per sequence) and the comparison to be made (second to last tone with first tone or last tone with first tone) varies across sequences to reduce the possible inattention to intervening tones. The sequence length is kept constant for the 6 and 7 tone sequences by introducing a short pause prior to the first tone for the 6 tone sequences. No analysis is planned to compare the 6-tone with the 7-tone conditions. Subjects will be asked to keep their eyes open and fixate a cross in the middle of the screen that will be only interrupted for the short visual prompt. All subjects should be made familiar with the pitch memory task for approximately 10 min prior to the actual MR session using samples of the stimulation material. All subjects should perform above chance in the pre-fMRI training phase. The behavioral performance during the fMRI session will be calculated as correct responses (in %).

A pilot study was designed to assess whether the design of this task fulfills the aforementioned requirements of the experimental task.

5.3 Pilotstudy: Auditory Learning

In order to assess whether the chosen differences in frequency and number of distractors yield the expected results, five subjects were tested once (initial baseline) and then retested three times within one week period using the above designed pitch memory task.

All subjects performed above (or close to) change in the initial baseline test (Table 1). Their scores were in a range of 48.75% -85% correct. None of the subjects had musical training. In this initial baseline test, the variability among subjects suggested that performance differences exist even within a group of non-musicians. This finding might be explained by differences in auditory processing between strong and weak performer. The results showed no significant differences between the condition with four distractor tones and five distractor tones.

After being retested three times, only one subject showed a ceiling effect while the rest of the subjects improved their scores in comparison to the initial baseline test.

The task tested in this pilot study fulfilled the requirements of the experimental task and will therefore be used as the experimental task in the fMRI design.

5.4 The motor control task

In order to assess brain activation due to the experimental task, one hast to contrast those images to a baseline condition. The experimental task utilized here essentially included three phases. The first phase is the 'auditory phase', wherein subjects listen to the presented tones and try to remember the first one. During the second phase, referred to as the 'judgment phase' subjects receive the prompt visually and determine whether or not the two target tones are identical. The last phase, which requires subjects to press a button based on their decision in the 'judgment phase', can be described as the 'button press phase'. In order to assess the 'auditory phase' without any interference of visual stimulation and button pressing, a control task, which contains and controls those components, is necessary. The control task employed here is a rest condition (no auditory stimulation) with the same eye fixation requirement used in the pitch memory task (Figure 9A). Subjects will also be asked to press a button depending on a short visual prompt ("right" or "left"), which will be very similar to the one in the pitch memory task.

6. The fMRI design – modifying the sparse temporal sampling method

6.1 FMRI scanning parameters

As already discussed in chapter 3, auditory tasks in the MR environment have been regarded as challenging because of the noise created by the gradient coil switches. This "scanner noise" can (1) interfere with the auditory stimulation (Bandettini et al., 1998; Shah et al., 1999, 2000; Hall et al., 2000), (2) lead to masking of the auditory cortical response depending on the frequency of the MR acquisition, (3) cause activation of the auditory cortex itself depending on the effective repetition time (TR) for MR acquisitions (Bandettini et al., 1998; Scheich et al., 1997; Ulmer et al., 1998), and (4) cause variations in the attentional demands if frequency and intensity of the MR scanner noise differ among studies. A few imaging designs have been proposed to overcome these interferences (Edmister et al., 1999; Hall et al., 1999, 2000). Hall et al. (1999) compared continuous scanning with a sparse temporal sampling method, using an effective repetition time (TR) of 14s and revealed a greater MR signal change for acquisitions with a long TR. Additionally, this study revealed, that if scanner noise is recorded and played back for the subject, a signal change of up to 1.5% could occur in primary and secondary auditory cortices. Hall et al. (1999, 2000) showed further that activation peaked 4-5 s after stimulus onset and decayed after an additional 5-8s. Others have shown a decrease in the spatial spread and lower z-scores of the activated auditory regions dependent on the duration of the MR scanner noise (Shah et al., 1999). Belin et al. (1999) used an effective TR of 10s and varied the delay between a short auditory stimulus and the MR acquisition. The response of the primary auditory cortex peaked approximately 3s after stimulus onset and lasted for 3s.

Here, a variation of Halls' (Hall et al., 1999) and Belins' (Belin et al., 1999) method of sparse temporal sampling was used to examine MR signal changes related to a pitch memory task (see Figure 9A)

Functional magnetic resonance imaging (fMRI) was performed on a Siemens Vision (Siemens, Erlangen, Germany) 1.5 Tesla whole-body MRI scanner, equipped with echo planar imaging (EPI) capabilities using the standard head coil for radio-frequency (RF) transmission and signal reception. A gradient-echo EPI–sequence with an effective repetition time (TR) of 17s, an echo time (TE) of 50ms and a matrix

of 64x64 was used. Using a midsagittal scout image, a total of 24 axial slices 4x4x6 mm voxel size) - parallel to the bi-commissural plane - were acquired over 2.75s each 17s. Initiation of the first set of 24 slices was triggered by a TTL pulse from a PC and all subsequent MR acquisitions were synchronized with stimulus presentation. A high resolution T1 weighted scan ($1mm^3$ voxel size) was acquired for each subject for anatomical co-registration.

Using a variation of the sparse temporal sampling method, one set of 24 axial slices was acquired every 17s to circumvent the scanner noise interferences. Although the TR remained constant at 17s, the delay between the end of the stimulation and the onset of the next MR acquisition varied as the auditory stimulation frame moved within the 17s time frame (see Figure 9B). There was a minimum delay of 0s and a maximum delay of 6s between the end of the auditory stimulation and the onset of the MR acquisition (see Figure 9B). These imaging time points (ITP) will be referred to as ITP0 through ITP6. Between the end of the MR acquisition and the onset of the next auditory stimulation, there was a minimum delay of 4s and a maximum delay of 10s. Using this method, the time course of processing the pitch memory task can be revealed.

7. Study A:

The functional anatomy of pitch memory-an fMRI study with sparse temporal sampling

7.1 Specific aims for study A

Aim 1: *Assessment of the time course of functional anatomy of the designed pitch memory task over a 6 second time window.*

Aim 2: *Assessment of performance related differences of the functional activation pattern of the designed pitch memory task.*

Aim 3: *Evaluation of the modified sparse temporal sampling technique*

7.2 Introduction

The functional anatomy of pitch memory has not been thoroughly and there are discrepancies comparing some of the experimental animal studies and the few neuroimaging studies in humans that have examined pitch memory. Deficits in tonal retention and auditory memory were seen after bilateral ablations of the superior temporal cortex in monkeys, whereas unilateral cortex lesions resulted only in minor auditory memory deficits (Stepien et al., 1960; Colombo et al., 1990, 1996) but usually no impairments in frequency discriminations. There is also a growing body of literature, which suggests that extratemporal brain regions within the dorsolateral and ventrolateral prefrontal cortex may serve a function during the retention of an auditory stimulus (Gottlieb et al., 1989; Bodner et al., 1996; Romanski & Goldman-Rakic, 2002).

To date, human functional imaging studies that have assessed pitch processing or auditory short-term working memory have not disclosed a consistent pattern of activation across the studies. In a positron emission tomography (PET) study, Zatorre et al. (1994) revealed blood flow increases bilaterally in the superior temporal cortex (with an inclination for the right side) when subjects listened to melodies. When subjects were asked to perform a pitch memory task in contrast to a passive listening

task, a right inferior frontal region became activated indicating an involvement of frontal regions in auditory working memory.

Griffiths et al. (1999a) found a more extensive right lateralized network including cerebellum, posterior temporal and inferior frontal regions when subjects were asked to make a "same/different" judgment while comparing pitch sequences of 6 tones. More left hemispheric activation in the precuneus, superior temporal gyrus, and superior frontal gyrus were found in a study by Platel et al. (1997) in which subjects were asked to detect pitch changes in familiar tunes. Celsis and colleagues (1999) found rightward asymmetry of the primary and secondary auditory cortex for tones, but left more than right posterior temporal lobe activation when subjects were presented with deviances in the tonal sequences. It is most likely that frontal/prefrontal as well as parietal lobe regions play a common role in auditory working memory and in the online maintenance of tonal patterns (Chao & Knight, 1996; Celsis et al., 1999), recent experimental evidence even suggested that the prefrontal cortex has cells that respond to non-spatial auditory cues (Romanski & Goldman-Rakic, 2002). The role of the temporal lobe in auditory memory remains unclear. Several studies assessing the effects of lesions on melodic discriminations and pitch judgments found impairments mainly after right but not left temporal lesions or temporal lobectomies (Milner, 1962; Zatorre, 1985; Zatorre & Halpern, 1993; Samson & Zatorre, 1988).

The current study was undertaken to explore the functional anatomy of pitch memory in a group of subjects with minimal or no musical experience using a variation of a sparse temporal sampling technique. This technique allowed subjects to listen to the auditory stimulation without any scanner interference in order to examine the time course of cortical activation due to a pitch memory task.

7.3. Materials and Methods

7.3.1. Subjects

Eighteen normal right-handed volunteers (age range: 18-40; 9 female and 9 male) participated in the study after giving written informed consent. Subjects were unselected for musical training; most of them had received some musical theory classes, usually as part of their elementary, high school, or college education, but none were professional musicians and none of our subjects actively played any

instruments. They had no history of any neurological or hearing impairment. All subjects were strongly right handed according to a standard handedness questionnaire (Annett, 1970).

7.3.2. Experimental tasks (Figure 9A)

All subjects performed the pitch memory task' which was contrasted with the motor control task (for detailed description see section 5.2).

7.3.3. FMRI design and parameters

The in chapter 6 described fMRI scanning parameters and the modified sparse temporal sampling method was here used and will be evaluated.

The initial exploratory analysis of each imaging time point indicated that the pattern of brain activation varied depending on the delay between MR acquisition and the end of the auditory stimulation frame. However, the change between neighboring imaging time points was minimal which lead us to combine imaging time points into three combined clusters of time points to demonstrate the main activation changes over time; furthermore, this allowed us to have a higher number of acquisitions per combined time point for statistical reasons. MR acquisitions obtained at imaging time points 0-2s were combined into one block, MR acquisitions obtained at imaging time points 3-4s were combined into the second block and MR acquisitions obtained at imaging time points 5-6s were combined into the third block.

7.3.4. FMRI data analysis

FMRI data were analyzed using the SPM99 software package (Institute of Neurology, London, UK). Each set of axial images for each subject was realigned to the first image, co-registered with the corresponding T1-weighted data set, spatially normalized to the SPM99 template using a non-linear spatial transformation with 7x8x7 basis functions, and smoothed with an isotropic Gaussian kernel (8mm full-width-at-half-maximum). Condition and subjects effects were estimated using a general linear model (Friston et al., 1995a,b). The effect of global differences in scan intensity was removed by scaling each scan in proportion to its global intensity. The pitch memory task was contrasted with the motor control task for these three clusters of imaging time points a threshold of $p< 0.05$, corrected for multiple comparisons (Worsley et al., 1996) was applied. In addition, these imaging clusters were also

contrasted with each other, using the contrast images to determine significant changes in the time course of the activation. Low frequency drifts were removed using a temporal high-pass filter with a cutoff of 200s. Because of the sparse temporal sampling design there is no temporal auto-correlation between the images. Therefore, the data were not convolved with the hemodynamic response function (HRF) and a low-pass filter was not applied.

In order to describe the time course of activation, regions of interests were drawn on a spatially standardized, group averaged anatomical dataset and superimposed on the SPM_T-images representing the group contrasts "pitch memory versus motor control" for each single imaging time point. Anatomical regions were drawn on each hemisphere and included the first transverse gyrus of Heschl representing primary auditory cortex, the planum temporale (for definition see Steinmetz et al., 1991 and Schlaug et al., 1995b) representing auditory association cortex, the supramarginal gyrus, and lobules V and VI of the cerebellum (Schmahmann et al., 1999).

The relationship between performance (% correct responses) and task-related activations was examined by weighting the parameter estimates with the performance data of each subject, which were normalized to the group mean performance.

7.4 Results

7.4.1 Behavioral results

All subjects performed above chance in the pre-fMRI training phase. The behavioral performance during the fMRI session was calculated as correct responses (in %). All subjects performed above chance in the pitch memory task. The mean of correct responses was 66.8% (SD 11.1; range: 54-100%).

7.4.2. Time course of activation pattern: *Comparing pitch memory with control condition for three combined imaging time points*

The brain activation pattern during combined imaging time points 0-2 (0-2s after end of stimulation) is dominated by strong and extensive - left more than right - activation of the superior temporal gyrus bilaterally including Heschl's gyrus (HG) and auditory association cortex, anterior, lateral and posterior to Heschl's gyrus including the planum temporale (PT), and there was also activation of the supramarginal gyrus (Figure 10). Activations outside the perisylvian region included a left posterior

dorsolateral frontal (-43.0, -7.2, 43.2) and right posterior dorsolateral frontal region (43.2, 2.5, 41.9), a superior parietal region on the right side (44.9, -44.0, 43.1), a left>right pre-SMA region (-0.8, 4.4, 45.5), and lobules V and VI of the cerebellum on the left side (-23.6, -67.3, -24.9) (Figure 10).

The brain activation pattern at combined imaging time points 3 and 4 (3-4s after end of stimulation) showed prominent activation of the left lateral superior temporal plane and of the right planum polare, but no significant activation of Heschl's gyrus anymore. There was still strong activation of cerebellar lobules V and VI bilaterally (left more than right). There was some scattered activation involving a posterior dorsolateral frontal region (left hemisphere) and a superior parietal region (both hemispheres), which were seen in the initial time points as well. There was also activation of the left inferior frontal operculum, including Broca's region (-51.8, 6.4, 24.5), and an adjacent activation in the left lateral mid-dorsal prefrontal cortex (-41.2, -7.2, 44.9) (Figure11).

The brain activation pattern at combined imaging time points 5 and 6 (5-6s after end of stimulation) showed prominent activation of cerebellar lobules V and VI on both sides, the anterior superior parietal region on the right, and the planum polare region bilaterally (Figure 12).

7.4.3. Contrasting early with late activations

Contrasting the initial imaging time points (0-2s after the end of auditory stimulation) with the intermediate (3-4s) as well as with the late imaging time points (5-6s) revealed extended significant ($p < 0.05$, corrected) activations of the superior temporal gyrus bilaterally for both contrasts (Figure 13). In addition, activation of the anterior frontomesial region (-4.3, 4.4, 47.3) was seen bilaterally in the contrast "initial time points vs late time points". The differences in the superior temporal gyrus are consistent with results from our ROI analysis (Table 2) which showed higher t-values for HG and PT in the first time point cluster and then a continuous decrease at later imaging time points reaching negative values after imaging time point 4 (Table 2). Mean regional t-values were overall greater for the left hemisphere for the first three imaging time points (Table 2). The planum temporale region, representing auditory association cortex, showed a slight rise in mean t-values on the left reaching the highest t-values at the second imaging time point for both hemispheres, again higher t-values were seen for the left hemisphere region. Mean regional t-values in the PT

region decreased gradually reaching negative t-values at time point 4 for the right hemisphere and time point 5 for the left hemisphere. The regional analysis for the SMG showed the highest mean t-values at the second imaging time point (one second after the end of the auditory stimulation) and a rapid decline over time in the right SMG while the left SMG showed positive t-values up to imaging time point 6 indicating a longer involvement of the left supramarginal gyrus in the pitch memory task.

By contrasting the intermediate imaging time points (3-4s) with the late imaging time points (5-6s) a small cluster of significant voxels were seen in the right (55.5, -31.5, 7.1) and left superior temporal gyrus region (–57.4, -36.8, 6.8) (Figure 13). The contrast of the intermediate time points (3-4s) to the earlier ones (0-2s) revealed no significant differences.

By contrasting the last time points (5-6s) to the initial time points (0-2s) bilateral activation of the dorsolateral cerebellum was seen (Figure 13), further supporting the strong activation of the cerebellum throughout the task. Similar results were seen in the regional analysis (Table 2). The contrast of the last imaging time points (5-6s) to the intermediate imaging time points (3-4s) showed no significant differences.

7.4.4. Correlating performance with brain activation pattern

By weighting the parameter estimates with the mean corrected performance data of each subject, activity in the SMG emerged as positively correlated with higher accuracy in the pitch memory task (Figure 14 A, B). The left SMG (-44.8, 42.1, 20.3) was much more dominantly activated than the right SMG (55.5, -34.3, 13.6). The supramarginal gyrus on the left also stayed active during the intermediate imaging time points (3-4s after the end of the auditory stimulation). At the last imaging time points (5-6s after the end of the auditory stimulation), there was prominent activation of the left cerebellum including the posterior part of lobule VI (-16.6, -72.9, 23.9; Figure 14 C, D).

A negative correlation between activity and performance in the pitch memory task was found in the right temporal-occipital junction (53.7, -51.8, 0.5) for the initial imaging time points and in the left superior parietal lobe (-28.9, -57.6, 44.1) at the last two imaging time points (Figure 14 E, F).

7.5 Discussion

By refining a sparse temporal sampling technique as originally developed by Hall et al. (1999), this study's facilitators investigated the functional anatomy and the time course of cerebral activations of a pitch memory task. The use of a sparse temporal sampling technique enabled circumvention of interferences of scanner noise and auditory tasks (Hall et al., 1999; Belin et al., 1999; Edmister et al., 1999; Shah et al., 2000). The majority of previous studies using a sparse temporal sampling technique only examined responses in primary and secondary auditory areas, most typically using short stimuli such as single tones. Belin et al. (1999) assessed the time course of primary auditory cortex activation with an event-related method. Maximal signal change occurred 3s after stimulus onset and lasted for 3s. The earliest imaging data in this study were obtained at 4.6s after the start of the auditory stimulation. No MR acquisitions were obtained before 4.6s to minimize the possible interference between scanner noise and auditory task. This makes it likely that the maximal signal change in primary auditory cortex in this study could be earlier than 4.6s after stimulus onset. It is also possible that the time course of the cerebrovascular response in primary and secondary auditory cortex to a single tone differs from that of a sequence of tones. Robson et al. (1998) showed that the fMRI response to sequences of 6s and longer are linear but that shorter stimuli produce signals that are larger than might be expected from the results of the longer stimuli. The responses in Heschl's gyrus in this study are in partial agreement with Hall et al. (2000) who reported maximal activity change in response to recorded MR scanner noise to occur between 4-5s after stimulus onset and to decay 5-8s later. The decay of significant activations occurred slightly faster in this study compared to Hall et al. (2000).

The planum temporale - a representative anatomical region for secondary auditory cortex - showed a maximal signal change between 5-6s after the beginning of auditory stimulation and the signal decayed 3-4s later. Similar activations of the PT have been seen in other studies using either single tones or musical sequences (Binder et al., 1996; Ohnishi et al., 2001). The SMG showed the highest T-values between 5-6s after the beginning of the auditory stimulation in both hemispheres. However, there was stronger activation on the left compared to the right SMG and the decay was different for right and left hemisphere. While activity in the right SMG decayed relatively fast, the left SMG remained active for a longer period of time.

The strong leftward activation pattern is somewhat different to other studies showing a more rightward activation pattern in pitch memory tasks (Zatorre et al., 1994; Griffiths et al., 1999a). It is not very likely that the subjects were able to verbally encode the target tone, since none of them possessed absolute pitch and it would be very difficult for a subject without absolute pitch to develop a verbal labeling scheme during the course of this task. In similar experiments, Siegel (1974) and Zatorre & Beckett (1989) found that subjects without absolute pitch most likely use a sensory encoding strategy. This sensory encoding strategy may be visual, kinesthetic, or auditory. It is also unlikely that the visual prompt shown at the end of the auditory stimulation could have caused the left-sided activation, since the inherent cerebrovascular delay in response to a visually presented verbal command would have caused a left temporal lobe activation at the last imaging time points, but this was not seen. A more convincing explanation for the left more than right activation pattern is the possibility that a top-down processing stream could influence the activation pattern; a higher order brain region (e.g., SMG) could specify the area of processing at earlier imaging time points during the perceptual phase of this task. This explanation has some support in the here presented data, since the SMG on the left was more strongly activated than the SMG on the right and seemed to play a key role in those individuals performing well in the pitch memory task. The SMG could serve as a top-down modulator causing stronger involvement of left than right temporal regions. Several neurophysiological and lesion studies revealed the importance of the SMG - particularly on the left - for short-term auditory-verbal memory processes and phonological storage (e.g. Salmon et al., 1996; Sakurai et al., 1998; Vallar et al., 1997; Caplan et al., 1995; Paulesu et al., 1993; Clarke et al., 2000). The here presented study and those of others indicate that the SMG may be involved in short-term memory processes for musical information as well. Celsis et al. (1999) showed left SMG activation in a task requiring memory judgments between tones of different pitch height or spectral content.

The dominant dorsal cerebellar activation in the here used pitch memory task was surprising, although in agreement with reports indicating that the cerebellum has non-motor functions (Bower, 1997; Jueptner et al., 1997c; Parsons & Fox, 1997; Desmond et al., 1998; Penhune et al., 1998; Satoh et al., 2001; Schmahmann & Sherman, 1998). Several studies have shown now an involvement of the cerebellum in auditory tasks such as the planning of speech production (Silveri et al., 1998),

auditory verbal memory function (Grasby et al., 1993), tone recognition tasks (Holcomb et al., 1998) as well as musical tasks such as musical tempo and duration discrimination (Parsons, 2001). Furthermore, patients with degeneration of the cerebellum were found to be impaired in pitch discrimination tasks (Parsons, 2001). In study A, the cerebellum may be involved in the ongoing activity of pitch discrimination while subjects perform the pitch memory task. This could explain the cerebellar activation in the initial time points as well as throughout the task (see Figure 13 and Table 2). Furthermore, the strong correlation between activation and accuracy underlines the importance of the cerebellum for this pitch memory task. The superior parietal lobule was activated more prominently during the initial imaging time points. The superior parietal lobe may actually serve two functions in this task. Converging evidence from several studies have shown that the superior parietal lobule is an important nodal point for integrating multi-modal sensory information and for providing guidance to motor operations through intense reciprocal connections with the premotor cortex (Friedman & Goldman-Rakic, 1994; Bushara et al., 1999). Thus, requiring a motor response to an auditory cue could involve the superior parietal lobule. Neuropsychological and functional imaging evidence also suggest that the parietal lobe, in particular the right parietal lobe, is a key part of a larger network involved in auditory spatial and attentional functions (Clarke et al., 2000; Bushara et al., 1999; Griffiths et al., 2000; Weeks et al., 1999). Satoh et al. (2001) compared a harmony listening condition with a more specific alto-part-listening condition and found bilateral increases in the superior parietal lobules among other changes using positron emission tomography. Their interpretation that the parietal lobules are involved in auditory selective attention as well as the analysis of pitch information on a mental score is supported by other work showing that selective auditory attention lead to significant activation of the superior parietal lobe (Pugh et al., 1996). Of interest is that better performance in the pitch memory task was associated with less activation of the left superior parietal lobule and of a region in the temporo-occipital junction. This might indicate that subjects with an overall better task performance might rely more on short-term auditory memory storage (involving the SMG) than on multi-sensory integration of information (involving the superior parietal lobule).

The initial and intermediate imaging time points in this pitch memory task also showed strong activations of the inferior frontal gyrus on both sides. Although neuroimaging studies have shown the involvement of the inferior frontal lobes in

auditory processing and auditory working memory (Chao & Knight, 1996; Griffiths, 2001; Zatorre et al., 1994), the role that these regions play in auditory processing remains largely unclear. Several physiological studies of the frontal lobe in non-human primates have focused on auditory spatial processing in the dorsolateral prefrontal cortex, although the ventrolateral prefrontal cortex might also play a role, since it receives afferents from auditory cortex, as has been shown in monkeys. Romanski & Goldman-Rakic (2002) recorded neuronal responses to auditory cues in awake monkeys from ventrolateral prefrontal cortex. The localization of auditory responses in the ventral prefrontal cortex in the macaque brain is suggestive of some functional similarity between this region and the inferior frontal gyrus of the human brain (including Broca's area), where mnemonic, semantic and syntactic auditory processes have lead to brain activation. Griffiths (2001) suggested that the features of individual notes are analyzed in the pathway up to and including the auditory cortices, while higher-order auditory patterns and information is analyzed by distributed networks in the temporal lobe and frontal lobes distinct from the auditory cortices. Zatorre & Belin (2001) suggested that processing of pitch patterns, such as occurs in melodies, require higher-order cortical areas, and interactions with the frontal cortex. The latter are likely related to tonal working memory functions that are necessary for the on-line maintenance and encoding of tonal patterns

In summary, this study showed that a distributed and dynamic brain network subserves pitch memory functions. The pitch memory task used in the here presented experiment relied more on left than right hemisphere regions. The supramarginal gyrus and the dorsolateral cerebellum seem to play a critical role, possibly as a short term pitch information storage site (SMG) and as a pitch discrimination processor (cerebellum). Both processes are of critical importance for the successful performance in this pitch memory task.

7.6 Short evaluation of specific aims for study A

Aim 1: *Assessment of the time course of functional anatomy of the designed pitch memory task over a 6 second time window*.

The pitch memory task employed in this study was designed and piloted based on criteria described in detail in chapter 5. The study A could clearly reveal the functional anatomy of pitch memory during a 6 second time frame. The ITPs could be

divided into three major clusters, which demonstrate the processing stages of the given task. The used ROI analysis exposed time course distinctions relative to different areas of the brain. Further studies should consider different ITPs when planning their experimental designs. This method can provide useful and important information regarding successive brain processing stages and can help to overcome the lack of temporal information in fMRI.

Aim 2: *Assessment of performance related differences of the functional activation pattern of the designed pitch memory task.*

One criterion for the here used pitch memory task was that the initial performance of all subjects is above chance (%). The performance score of the subjects in Study A averaged out to 66.8% (SD 11.1; range: 54-100%). Furthermore, a correlation analysis disclosed performance related differences in the left supramarginal gyrus. These differences are important for subsequent studies (see chapter 8 and section 14.1). In order to assess performance related changes in auditory areas in response to a one week training, one had to assess the performance sensitivity of the tasks employed prior to the training.

Aim 3: *Evaluation of the modified sparse temporal sampling technique*

A sparse temporal sampling technique originally developed by Hall et al. (1999) was redefined and modified. Using this method made it possible to discern the functional anatomy and the time course of cerebral activations of a pitch memory task. The use of a sparse temporal sampling technique helped to override some of the interferences of scanner noise and auditory tasks (Hall et al., 1999; Belin et al., 1999; Edmister et al., 1999; Shah et al., 2000). Most of the previous studies that employed a sparse temporal sampling technique only examined cortical responses in primary and secondary auditory areas, typically using short stimuli such as single tones. The developed here, however, could disclose the activation pattern of the given pitch memory task over a 6 second interval as well as over the whole brain space, therefore revealing the complete functional network.

8. Study B:

Performance related changes in the auditory cortex- an fMRI training study

8.1 Specific aims for study B

Aim1: *Assessment of training induced functional plasticity in the auditory cortex and extratemporal brain regions*

Aim2: *Assessment of the influence of performance improvement on training induced functional changes in auditory and extratemporal brain regions*

Aim3: *Assessment of training induced functional plasticity in the auditory cortex in the absence of the scanner background noise*

8.2 Introduction

The neural effect of auditory learning studies in humans have not been studied and described as thoroughly as neural effects of learning in other domains (e.g., motor skills) have been. Motor learning studies have some divergent results with regard to whether learning is associated with activity increases or decreases or both (Jenkins et al., 1994; Schlaug et al., 1994; Jueptner et al., 1997a,b, c; Toni et al., 1998; Karni et al., 1995, 1998; van Mier et al., 1998; Doyon et al., 1996; Hazeltine et al., 1997; Grafton et al., 1995). Some studies have shown a learning-related MR signal increase during the initial learning phase and more ambiguous trends in the subsequent and later stages, which were characterized by MR signal decreases and fewer persistent signal increases in the 'overlearned phase', respectively when the performance score indicated a behavioral ceiling effect (e.g., Toni et al. 1998). Furthermore, several studies revealed changes in other brain regions than motor related regions, e.g. cognitive areas are being involved in motor learning (e.g. Muller et al., 2002; Sakai et al., 2002).

The few auditory learning studies performed to date have failed to provide a cohesive picture (Cansino & Williamson, 1997; Menning et al., 2000; Jancke et al., 2001), which has resulted in continuing uncertainty with regard to which auditory brain regions are modulated by auditory learning and the direction of this modulation. Moreover, it is unclear whether auditory learning effects are apparent in more distant, polymodal association regions, or only evident in traditional auditory regions.

Animal studies (e.g. Recanzone et al., 1993) have typically revealed an increase in the cortical representation of the trained frequency as a result of auditory learning (e.g. frequency discrimination). Some studies have also shown a correlation between the cortical representation and the performance improvement (Recanzone et al., 1993). Nevertheless, changes in other extratemporal brain regions were not assessed, and lesion studies were restricted predominantly to lesions of primary and secondary auditory areas.

A few studies assessed nonverbal auditory training in humans using MEG, EEG or fMRI. Those studies showed a strong relationship between intensive frequency discrimination training and the corresponding functional MEG (Cansino & Williamson, 1997; Menning et al., 2000) and fMRI (Jancke et al., 2001) correlates. These studies revealed both signal increases and decreases in auditory, which are related to the behavior performance score in the given task in one study (Jancke et al., 2001), following the training period. Nevertheless, these studies have some limitations. First, extratemporal areas that could be involved in auditory learning are not assessed. Furthermore, differences in the experimental paradigms, methods, number of subjects, and amount of training make it difficult to reach firm conclusions about the neural correlates of non-verbal auditory learning. Additionally, the lack of both behavioral correlates and a control group in some of this studies makes it difficult to correlate behavioral change with brain change and differentiate test – re-test effects from changes that result from learning. A recent study (Gaab et al., 2003a) noted a correlation between activation of the left supramarginal gyrus and the performance score for a pitch memory task. This attests to the importance of including behavioral scores in the analysis in order to determine regions involved in auditory perception and auditory learning and demonstrate the important role played by extratemporal regions in pitch memory processing.

The aim of this study was to improve upon these prior studies by assessing behavioral performance in the testing and training session and evaluating inter-individual differences in the neural effects of learning. In this study, an established pitch memory experiment (see chapter 5 and 7), which contains perceptual as well as pitch memory aspects was employed in order to obtain training-related changes in auditory and extratemporal brain regions. Additionally, a sparse temporal fMRI technique (Hall et al., 1999, 2000; Bandettini et al., 1998; Edmister et al., 1999) with

a jitter-like acquisition was employed in order to obtain training-related changes in auditory brain regions without interferences from the MR scanner noise.

8.3. Materials and Methods

8.3.1 Subjects

Twenty-four normal volunteers (age range: 19-34; 13 males) participated in the study after giving written informed consent. Subjects were unselected for musical training. Some of the subjects had musical theory classes, generally as part of their elementary, high school education, but none of the subjects were professional musicians or played musical instruments. They had no history of any neurological or hearing impairment. According to a standard questionnaire (Annett, 1970), all subjects were strongly right handed.

8.3.2 Experimental tasks (Figure 9A)

All subjects were scanned twice separated by 7 days while performing the pitch memory task, which was contrasted with the motor control task (for detailed description see section 5.2). Behavioral performance during the fMRI session was calculated in terms of the number of correct responses (in %). The error rate (in%) for the five different frequency distances (diff1 to diff5) and for the "same" condition was calculated separately.

8.3.3 Training (Figure15)

Fourteen of the subjects were randomly assigned to the training group. The training took place on 5 consecutive days in-between the two fMRI scanning sessions, beginning with the day following the first fMRI session (pre-training-fMRI) and ending the day prior to the last fMRI session (post-training-fMRI). Subject performed the aforementioned pitch memory task (section 5.2) for an hour with two short breaks in between. Training for the motor control task was not provided. The training duration was chosen based on previous auditory training studies. Menning et al. (2000) trained subject for three weeks but discrimination improved rapidly only in the first week of training with much smaller gains in the second and a almost stable performance rate in the third week. Jancke et al. (2001) showed significant activity changes after a one week training in an auditory oddball procedure. While performing

the task, subjects did not receive any feedback. However, they did receive feedback regarding their performance rate following each of the training session. This decision was made based on a study of Campell et al. (1963), who found a considerably poorer performance in a frequency discrimination training task for a group who had feedback during the session in comparison to a group who did not receive feedback about their performance.

8.3.4 FMRI design and parameters

The fMRI design and the modified sparse temporal sampling method (described in detail in section 6.1) were applied during the two scans.

8.3.5 FMRI data analysis

The SPM99 software package (Institute of Neurology, London, UK) was used to analyze fMRI data. Each set of axial images for each subject and each session (pre training and post training separately) was realigned to the first image. All images (pre and post training session combined) were then co-registered with the corresponding T1-weighted data set, spatially normalized to the SPM99 template using a non-linear spatial transformation with 7x8x7 basis functions, and smoothed with an isotropic Gaussian kernel (12mm full-width-at-half-maximum). Condition and subjects effects were estimated using a general linear model (Friston et al., 1995a,b). The effect of global differences in scan intensity was removed by scaling each scan in proportion to its global intensity. Low frequency drifts were removed using a temporal high-pass filter with a cutoff of 200s. Due to the sparse temporal sampling design there is no temporal auto-correlation between the images. Therefore, the data was not convolved with the hemodynamic response function (HRF) and a low-pass filter was not applied. The pitch memory task was contrasted with the motor control task in order to obtain contrast images for each of the three groups (for group description see section 8.4.1). Second-level analyses (t-tests) with the SPM contrast images for the three groups were subsequently performed.

8.3.6 Voxel-based morphometry

In order to analyze the structural data, an optimized method of VBM (Ashburner & Friston, 2000;Good et al., 2001a,b) that used the SPM99 package (Institute of Neurology, London, UK) was applied. The process of spatial normalization to the

standard anatomical space was performed in a two phase. First, each image was registered to the International Consortium for Brain Mapping (ICBM) template (Montreal Neurological Institute, Montreal, Canada), which approximates Talairach space. A 12-parameter affine transformation was then applied in order to correct for image size and position. Regional volumes were preserved while global differences in total brain volume were corrected. The normalized images of the control subjects only were averaged and smoothed with a Gaussian kernel of 8 mm full-width at half-maximum (FWHM) and subsequently used as a new template with reduced scanner- and population-specific bias. In the second step of the normalization process, each image was locally deformed to the new template using a non-linear spatial transformation. This accounts for the remaining shape differences between the images and the template and improves the overlap of corresponding anatomical structures. Finally, normalized images were corrected for non-uniformities in signal intensity and partitioned into gray and white matter, cerebrospinal fluid, and background using a modified mixture model cluster analysis. In order to remove unconnected non-brain voxel (e.g. rims between brain surface and meninges), a series of morphological erosions and dilations were applied to the segmented images (Good et al., 2001a,b). A Gaussian kernel of 12 mm FWHM was used to smooth the resulting gray and white matter images. Voxel-by-voxel t-tests, using the general linear model, were employed in order to search for gray or white matter differences between the "strong" and "weak" learner (see section 8.4.1) groups.

8.4 Results

8.4.1 Behavioral results

All subjects performed above chance in the first fMRI pre training session. An initial analysis of improvement scores (post training session – pre training session) across the entire group indicated a high interindividual variability with improvement scores ranging from -2% to +19%. These results indicate the need of two subgroups, those that showed a large improvement and those that exhibited either a minimal improvement or no improvement at all.

A K-Means Cluster Analysis was performed with the intent to delineate two subgroups, a "strong" learner and a "weak" learner group. After two iterations the analysis revealed two clusters with seven subjects in each cluster (Table 4). The

"strong" learner group showed a cluster center of 15.29% (improvement score) while the "weak" learner group revealed a cluster center of 4.79% (Table 5 and Table 6). The subgroups differed significantly from one another in a two-sample t-test (T=(5.98), p< 0.000). A separation into three groups did not reveal any useful results, since one cluster contained 10 subjects (cluster center: 8.65) whereas the other two clusters consisted of three subjects (cluster center: 18.67) and one (cluster center: -2). An ANOVA with group as a factor revealed a significant difference between the three groups for the improvement scores and post-hoc t-tests showed a significant difference between the "strong" and the "weak" learner as well as between the "strong" learner and the control group. There was no significant difference between the "weak" learner group and the control group (Table 9-11). However, the "strong" and "weak" learner group differed significantly in their performance scores on each day of their respective training sessions (Day1 through Day5) and for the behavioral data obtained during the post-training fMRI experiment (Table 7). No between group differences were found prior to the training sessions for the three groups (Table 8). The control group showed a performance score of 0.4% (SD = 8.65).

A further analysis was performed to obtain training effects for each of the five frequency distances (diff1 to diff5) and the "same" condition separately (Table 12) Therefore the error rate in percent for each of the frequency distances and the "same" condition for the pre-and posttest was calculated. Then paired sample t-tests (pre training test versus post training test) of the error rates for each of the frequency distances and the same condition for each group were performed separately. The "strong" learner group showed a significantly better performance for the "same" condition, the diff1 (41.17 Hz) and diff2 (44.64 Hz) condition. The other two frequency distances (diff3, diff4 and diff5) showed a positive, but non-significant trend. The "weak" learner group did not show any significant difference in their error rates for either the same or the different conditions.

8.4.2. FMRI results

8.4.2.1 Effects at baseline

All three groups (control group, "weak" learner, and "strong" learner) demonstrated a similar activation pattern at the first fMRI scan (see "learner group combined in Figure 16). The activation pattern for the contrast pitch memory > motor control revealed extended activation of the superior temporal gyrus including bilateral

activation of the primary and secondary auditory cortex and the superior temporal sulcus. In addition, there were bilateral activation of the superior parietal region, the posterior inferior frontal gyrus, the postero-lateral cerebellum and the SMA.
Comparing the "strong" learner group with the "weak" learner group as well as each of the learner groups with the control group using the fMRI data at baseline did not reveal any significant differences ($p>0.05$, corrected for multiple comparisons).

8.4.2.2 Effects in the "strong" learner group

Contrasting the post training session with the pre training session in a random-effects analysis revealed significant differences in primary and secondary auditory areas (-47.18/-33.8/17.32; 51.3/-33/17.36), the anterior part of the left supramarginal gyrus, the posterior part of the left insula cortex (-35.3/-21.6/6.8), and bilateral activation of the posterior cingulate and posterior parahippocampal gyrus.

The reverse contrast (pre-training> post-training) showed positive changes in the superior parietal lobe but more one the right (40.5/-53.7/ 41.3) than on the left (–42.3/50.1/42.3).

When the post>pre training contrast was compared between the "strong" learner and "weak" learner group ("strong" learner group (post>pre contrast) > "weak" learner group (post>pre contrast)), the anterior part of the supramarginal gyrus (-44.8/ -32.4/-20.5: Figure 17) as well as the right declive of the cerebellum (6/-65/-24; FDR corrected) showed a significant positive change. Comparing the pre>post contrast images between those two groups showed a positive effect in the right superior parietal cortex (36.1/-51.8/-54).

8.4.2.3 Effects in the "weak" learner group

Comparing the post-training with the pre-training session in a random-effects analysis revealed positive changes in the lingual gyrus bilaterally (16.8/-49.8/2.3), the left medial frontal gyrus (-11/45.1/10.6), the inferior frontal gyrus bilaterally (29.12/29.66/-14.7 and –27.2/27.2/-11.3), and the left parahippocampal gyrus (-32.4/-16.9/-13.6) (Figure 18). The reverse comparison (pre-training > post-training revealed positive changes in the anterior cingulate (-0.8/-20.1/36).

The anterior cingulated region (Figure 20) showed a significant positive change when the post>pre training contrast was compared between the "weak" learner and the "strong" learner group ("weak" learner" group (post>pre contrast) > "strong"

learner group (post>pre contrast)). Comparing the pre>post contrast images between those two groups showed a positive effect in the inferior frontal gyrus bilaterally, left more than right (Figure 20) ("weak" learner" group (pre>post contrast) > "strong" learner group (pre>post)).

8.4.2.4 Changes in the control group

Comparing scan 2 with scan 1 within the control group showed changes in the right pre-frontal cortex (27.4/12.7/22.4; Figure 19) when performing a random-effects analysis. No significant changes were detected comparing scan 1 with scan 2

8.4.3. Voxel based morphometric analysis between "strong" and "weak" learner

In order to exclude structural differences between the "strong" and "weak" learner group as a possible factor contributing to the differences in learning related changes, a voxel-based morphometry analysis was performed (Ashburner & Friston, 2000). This method was performed in order to search across the whole brain space for group differences in gray or white matter volume. No significant structural differences ($p < 0.05$, corrected) were found in regional white or gray matter volume between the "strong" learner and "weak" learner group.

8.5 Discussion

The results of this study suggest a change in the functional activity pattern in auditory temporal as well as auditory-related extratemporal brain regions after one week of training in a nonverbal auditory task. These changes are strongly correlated with the improvement score in the given training task. Previous studies in the auditory learning domain used pure perceptual tasks in order to access auditory learning. In one previous conducted study (Gaab et al., 2003a) that employed the same auditory paradigm, the time course of activation for this pitch memory task was revealed. Results suggest, that the task here used contains both auditory perception and auditory memory components. Moreover, this study reveals a positive correlation between task performance and activation pattern in the left supramarginal gyrus. In addition to changes in auditory areas, extratemporal changes were evident in this study following a week of training in this pitch memory task. These changes were strongly dependent on the improvement score in the auditory training.

The "strong" learner group showed positive changes in left hemispheric primary and auditory regions, including the planum temporale. Negative changes were seen in the superior parietal regions. In contrast, the "weak" learner group showed positive changes in extratemporal regions including bilateral changes in the lingual gyrus, inferior frontal gyrus, and left parahippocampal gyrus. Negative changes were seen in the anterior cingulated region. A control group was used to assess the test – re-tests effects of performing the pitch memory task twice, separated by a week without any training. Small positive changes were apparent in a right prefrontal region. When the post-training versus pre training fMRI imaged were contrasted between the "strong" and "weak" learner, the left supramarginal gyrus was the only region to show a significant difference.

8.5.1 Training effects in the "strong" learner group

The results indicate that left hemispheric auditory association areas, as well as posterior cingulate and parahippocampal gyrus show positive MR signal changes over time in those subjects that exceedingly improved in an auditory learning experiment. This increased activation was associated with a bilateral decrease of activation in the superior parietal lobe. Because none of the assessed subjects reached a performance score of 100% following the training session (no ceiling effect), the behavioral results indicated a significant improvement for this group but not an overlearned state.

Many studies showed the importance of auditory association areas in pitch perception and memory (e.g. Zatorre et al., 1994; Griffiths et al., 1999; Platel et al., 1997; Binder et al., 1996; Ohnishi et al., 2001). A recently conducted study that used the same stimulation task showed, among other areas, activation of the superior temporal gyrus and the supramarginal gyrus bilaterally, but more left more than right hemispheric (Gaab et al., 2003a). By regressing the performance score in the pitch memory task with task-related MR signal changes, the supramarginal gyrus (left >right) were significantly correlated with good task performance. Therefore, it is possible that the pitch memory training induced a shift to a more efficient network that primarily involved the necessary key regions (left hemispheric auditory association areas) that were integral to successful performance of the task.

The parahippocampal gyrus and posterior cingulate also demonstrated activity increases following the one week training period. This might also be the result of a training-induced change in the functional pattern involving more memory and

attention related areas after the training. Further studies need to be conducted in order to determine whether those areas play an important role in learning the pitch memory task e.g. by training some subjects until they will reach a ceiling effect (automatic status).

In addition to the increased activity in certain areas in this study, bilateral decreases were evident in some areas as well. This finding is consistent with previous studies, which have shown decreased activation in parietal associative cortex following training in other domains. In an fMRI training study using a mirror reading task, Kassubek et al. (2001), showed a decrease in activation in Brodmann areas 6 and 17 following a training period. The authors discuss these results in terms of habituation in the course of increased familiarity with the general conditions, which may result in a non-specific decrease in activation and reduced arousal. In this study, the decrease of activation of Brodmann area 7 indicates increased efficiency of specialized mental transformation processes, which triggers a reduction in the effort to decode the pitch memory sequences and keep them in working memory. Several other studies (Jenkins et al., 1994; Petersen et al., 1998; Petersson et al., 1999) also support this study's findings. Peterson et al. (1999) interpret their results with automaticity following training, i.e. reduced dependence on attentional and working memory resources as a consequence of practice.

Overall, one can assume that cerebral activity changes in parietal (more right then left) areas are associated with learning, which refers to a subset of a more widely distributed network that is active when performing a novel task which requires new operations and mental sets in comparison to a more efficient network which is possibly induced by increased familiarity, reduced arousal, prior experience (e.g. expertise) and/or decreased dependency on attentional and working memory resources.

8.5.2 Training effects in the "weak" learner group

Unlike the "strong" learner group, the "weak" learner showed massive positive activity changes following the training in the lingual gyrus bilaterally, the left medial frontal gyrus, the inferior frontal gyrus bilaterally and the left hemispheric parahippocampal gyrus. Behavioral results indicated that this group improved in average only 4.78% (posttest-pretest), implying that the training period did not cause subjects to transcend their novice status.

Surprisingly, there were positive bilateral changes in the lingual gyrus. The activation of this region might be explained by a different degree of involvement of working memory. Ragland et al. (2002) showed lingual gyrus and orbitofrontal activation in an n-back task with increased working memory load. In a review on cortical plasticity and music, Rauschecker (2001) suggested that the anterior STG and the orbitofrontal cortex are responsible for the processing of complex auditory patterns. Additionally, several lesion studies have shown an involvement of the orbitofrontal cortex in various learning tasks (for a review see Rolls, 1999). Based on the reviewed literature, the author stated that orbitofrontal cortex has important functions in motivational behavior. In a study with rhesus monkeys, Oscar-Berman (1975) showed impairment of auditory discrimination following lesions to the ventrolateral-orbitofrontal cortex, and several studies on macaque monkeys revealed strong connection from auditory areas to the orbitofrontal cortex (Hackett et al., 1999; Cavada et al., 2000). Several studies have also revealed reciprocal connections between the orbitofrontal and the parahippocampal region (Deacon et al., 1983; Price et al., 1991).

Furthermore, the here presented results showed that the left parahippocampal gyrus was activated while contrasting the pre-training with the post-training scans. Numerous studies assessing auditory memory showed activation in the parahippocampal areas (e.g. Engelien et al., 2000; Grasby et al., 1993). One could argue, that the "weak" learner used a different network after the training period, which contains the orbitofrontal-parahippocampal connection.

In addition to the positive changes following the training period, a deactivation of the anterior cingulated could be revealed. Several studies found the anterior cingulate cortex being related to task difficulty (Barch et al., 1997; D'Esposito et al., 1995). In fact, the anterior cingulate has frequently been observed in working memory and related tasks (e.g. Carter et al., 1995, 1998; Cohen et al., 1994; Posner et al., 1994), and some studies indicate possible involvement of the anterior cingulate in error detection or compensation (Dehaene et al., 1994; Gehring et al., 1993). MacDonald et al. (2000) could show a dissociating of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. In a Stroop task version, the authors demonstrated that the left dorsolateral prefrontal cortex was involved in implementation of control while the anterior cingulate cortex played a role in performance monitoring. In a PET study, Raichle et al. (1994) found that the anterior cingulate was most active during naïve performance while performing a simple verbal

response selection task. Following a 15 minute training, activity in this region decreased. The authors suggest that the anterior cingulate may function as a component of an anterior attention system.

Overall, it appears that the subjects in the "weak" learner group altered their network for processing this pitch memory task and relied primarily on working memory areas and memory areas following the training period. However, those areas do not seem to be optimal or most efficient areas in which to perform t this particular task. This was also reflected in the behavioral results.

8.5.3 Repetition effect in the control group

Performance of the auditory task twice (control group) was associated with changes in the prefrontal cortex. Because of the involvement of brain regions commonly associated with working memory while performing the experiment a second time, one could argue, that this indicates a different strategy in performing the pitch memory task

Numerous fMRI studies in animal and humans have demonstrated activation of the dorsolateral prefrontal cortex (DLPFC) during task conditions that engage working memory (for reviews see e.g. Sakai, 2003; Kane & Engle, 2002; Funahashi & Takeda, 2002).

It is worth noting that when the first and second fMRI studies were compared, only the "weak" learner and the control group showed an increase in working memory regions, though the regions involved differ slightly. Overall, this strategy does not appear to be successful given that neither group's behavior score changed more than 5%.

8.5.4 Improvement effects in "strong" learner in comparison to "weak" learner

When the pre-training versus post-training images were contrasted between the "strong" learner and the "weak" learner group, the supramarginal gyrus on the left was strongly activated. Consequently, this region seems to be of critical importance when performance improvement in auditory learning is correlated with imaging changes. This supports other studies, which implicate the posterior PT and SMG in various high order auditory processes. Several neurophysiological and lesion studies revealed the importance of the SMG - particularly on the left side- in short-term auditory-verbal memory processing and phonological "storage" (e.g., Salmon et al.,

1996; Sakurai et al., 1998; Vallar et al., 1997; Caplan et al., 1995; Paulesu et al., 1993; Clarke et al., 2000). Celsis et al. (1999) showed left SMG activation in a task requiring memory judgments between tones of different pitch height or spectral content. Furthermore, in a recent conducted study (Gaab et al., 2003a) revealed that by regressing the performance score in the same pitch memory task with task-related MR signal changes, the supramarginal gyrus (SMG, left > right) was significantly correlated with good task performance.

This study's findings suggest that auditory learning triggers the use of a more efficient network by increasing activity in key regions that are integral for pitch discrimination and pitch memory and decreasing activity in brain regions associated with attention and working memory. This effect is strongly correlated with the behavioral improvement in the auditory task. These results underscore the necessity of associating behavioral improvement with brain signal changes in order to determine learning associated changes. The results of this study support the "scaffolding" and "storage" framework by Petersen et al. (1998), which will be described in more detail in chapter 15.

8.6 Short evaluation of specific aims for study B

Aim1: *Assessment of training induced functional plasticity in the auditory cortex as well as extratemporal brain regions*

The here presented study B showed, that a one week auditory training can already lead to functional changes in auditory as well as extratemporal brain regions. Furthermore, activity decreases and increases in various brain regions could be revealed Interestingly, not only auditory areas were involved in the functional anatomy of pitch memory learning. Other, extratemporal areas, especially areas for higher order cognitive functions seem to play an important role in learning this particular task. Previous studies (Menning et al., 2000; Casino & Williamson 1997; Jancke et al., 2001) focused on functional short-term plasticity exclusively in auditory regions.

Aim2: *Assessment of the influence of performance improvement on training induced functional changes in auditory as well as extratemporal brain regions*

The results in this study suggest a change in the functional activity pattern in auditory temporal as well as auditory-related extratemporal brain regions after one week of training in a nonverbal auditory task which are strongly correlated with the improvement score in the given training task. The subjects, that improved in average 15% (Strong learner) showed positive changes in auditory areas as well as the left supramarginal gyrus After the one week training, the "weak" learner also showed changes of the functional activity pattern after the training but these changes were located in more memory related areas, e.g. parahippocampal gyrus. It seems, that these subjects changed their strategy and the underlying functional brain anatomy but the chosen strategy was not as efficient as the one of the "strong" learner. These results illustrate the importance of assessing behavioral correlates in learning studies.

Aim3: *Assessment of training induced functional plasticity in the auditory cortex in the absence of the scanner background noise*

Due to the modification of a sparse temporal sampling technique, auditory learning could be assessed in the absence of the scanner background noise. As described earlier, the assessing of auditory learning in the scanner environment is challenging due to the background scanner noise. So far, only one study has assessed functional changes due to short-term auditory training in the fMRI scanner.

The important question to ask is whether the cortex, and especially the auditory cortex shows the same properties of learning while being exposed to constant scanner noise in the background. One could argue that the neurons within the auditory cortex respond differently and therefore auditory learning might be reflected in a different way.

9. Study C:

The effect of musicianship on pitch memory in performance matched groups

9.1 Specific aims for study C

Aim1: *Assessment of the functional anatomy of pitch memory in professional musicians*

Aim2: *Assessment of the functional differences between professional musicians and non musicians in performance matched groups.*

9.2 Introduction

Pronounced functional differences were found between musicians and non-musicians in perisylvian brain regions using various brain mapping techniques (Altenmueller et al., 1986; Besson et al., 1994; Pantev et al., 1998; Trainor et al., 1999; Ohnishi et al., 2001; Schlaug et al., 2001; Zatorre et al., 1994). Increased musical sophistication was typically associated with more lateralized (mostly left) activation. However, it is unclear whether the between-group differences are due to differences in performance of experimental tasks (e.g., percentage correct answers), cognitive strategies, or even anatomical structures. Since the effect of performance differences between musicians and non-musicians can be controlled for by carefully matching the performance scores of both groups, the here presented study was designed to examine whether between-group differences in perceptual and/or cognitive strategies alone can explain functional brain differences between musicians and non-musicians. In addition, the influence of between-group structural brain differences on functional differences was assessed by measuring size and asymmetry of the planum temporale, a marker of hemispheric laterality.

The existing literature does not show a consistent pattern of brain activation in pitch memory or pitch discrimination experiments. When subjects listened to melodies, Zatorre et al. (1994) showed blood flow increases bilaterally in the superior temporal cortex (right more than left). A right inferior frontal region became activated when subjects were asked to perform a pitch memory task in contrast to a passive listening task. Griffiths et al. (2001) found a more extensive right lateralized network

including cerebellum, posterior temporal and inferior frontal regions when subjects were asked to make a same/different judgment while comparing pitch sequences of 6 tones. However, Platel et al., 1997 revealed more left hemisphere activations involving the precuneus, superior temporal and superior frontal gyrus when subjects were asked to detect pitch changes in familiar tunes. When subjects were presented with deviances in tonal sequences, Celsis et al., 1999 showed rightward asymmetry of the primary and secondary auditory cortex for tones, but left more than right posterior temporal lobe activation.

The aim of this study was to investigate the effect of musicianship on the neural activation pattern of a pitch memory experiment by selecting the high performing non-musicians from a larger group of subjects in order to achieve precisely matched groups of musician and non-musician. A pitch memory experiment was chosen since this is a challenging task for both groups and does not require any special musical knowledge. Since musicians with absolute pitch might use a different strategy in performing this task, only musicians who did not have absolute pitch were included.

9.3 Materials and Methods

9.3.1 Subjects

Twenty normal right-handed volunteers (age range: 18-40; 10 female and 10 male) without any neurological or hearing impairment, participated in this study after giving written informed consent. For this experiment, ‘musicians’ were defined as those who had formal music training and regularly played a musical instrument. None of the musicians had absolute pitch. A ‘non-musician’ was defined as someone who had never played a musical instrument and who had no formal musical training.

9.3.2 Experimental tasks (Figure 9A)

All subject performed were scanned while performing the in section 5.2 described pitch memory task which was contrasted with the motor control task. The behavioral performance during the fMRI session was calculated as a percentage of correct responses.

9.3.3 FMRI design and parameters

Functional Magnetic Resonance Imaging (fMRI) was performed on a Siemens Vision 1.5 Tesla whole-body MR scanner. To avoid interference with the MR scanner noise as well as auditory masking effects, a sparse temporal sampling fMRI method with an effective repetition time (TR) of 17 seconds was used. This ensured that the clustered volume MR acquisition was always separated from the actual auditory task. In addition, the stimulus-to-imaging delay time was varied between 0 to 6 seconds in a jitter-like fashion to explore the time course of brain activation in response to the perceptual and cognitive demands of this pitch memory task. Initiation of the first set of 24 slices was triggered by a TTL pulse from a PC and all subsequent MR acquisitions were synchronized with stimulus presentation. A high resolution T1 weighted scan (1mm^3 voxel size) was acquired for each subject for anatomical co-registration.

9.3.4 FMRI data analysis

FMRI data were analyzed using the SPM99 software package (Institute of Neurology, London, UK). After realignment, co-registration, normalization and smoothing (8mm full-width-at-half-maximum), condition and subjects effects were estimated using a general linear model (Friston et al., 1995a,b). The effects of global differences in scan intensity were removed by scaling each scan in proportion to its global intensity. The pitch memory task was contrasted with the motor control task and a threshold of $p< 0.05$, corrected for multiple comparisons was applied. Low frequency drifts were removed using a temporal high-pass filter with a cutoff of 200s. The data was not convolved with the hemodynamic response function (HRF) and a low-pass filter was not applied.

The imaging time points (ITPs) one through four (0-3s after the end of the auditory stimulation) and ITPs five to seven (4-6s after the end of the auditory stimulation) were combined into two blocks. This was done in order to (1) to achieve a higher number of events or acquisitions per block for statistical reasons, and (2) to reflect the main change over time in the activation pattern, since the initial imaging time points reflected more of a perception network while the later time points reflected more of a memory network. In the fMRI-analysis the pitch memory task was contrasted with the motor control task for these two combined clusters of imaging time points.

9.3.5 Morphometric assessment of brain laterality

One possible explanation for functional differences in perisylvian brain regions between musicians and non-musicians is a difference in brain anatomy. The planum temporale (PT) and the PT asymmetry can be used as a gross anatomical marker of perisylvian brain differences between the two groups. Previous studies revealed anatomical PT differences between musicians with and without absolute pitch (AP) (Schlaug et al., 1995b; Keenan et al., 2001), although \ differences in PT asymmetry between non-AP musicians and non-musicians in two separate studies were found. The surface area of the right and left planum temporale (PT) and its asymmetry score was determined for all subjects who participated in this study. The PT was defined according to previously published criteria (Schlaug et al., 1995b; Steinmetz et al., 1991) and the surface area was calculated as described in detail elsewhere (Keenan et al., 2001).

9.4. Results

9.4.1 Behavioral results

After individually matching non-musicians with musicians using task performance as the criteria, the musician group had a mean correct response rate of 78% (SD= 6) while the mean of the non-musician group was 76% (SD=6) ($p>0.05$).

9.4.2 FMRI results

In the pitch memory task, group mean activation images for both groups showed bilateral involvement of the superior temporal gyrus, supramarginal gyrus, posterior middle, inferior frontal gyrus and inferior/superior parietal lobe (Figure 21, 22). For imaging time points 0-3s (MR scans acquired 0-3s after the end of the auditory stimulation), contrasting the two groups (Figure 23, $p< 0.05$, FDR-corrected) revealed more activation of the posterior planum temporale and the supramarginal gyrus on the right and the superior parietal regions bilaterally in the musicians group. For the later imaging time points (4-6s after the end of the auditory stimulation), musicians showed more activation of right superior parietal region ($p< 0.05$, FDR-corrected; Figure 24). Lowering the statistical threshold ($p< 0.01$, uncorrected), revealed additional activation of the left supramarginal gyrus and the right inferior frontal gyrus in the musician group (Figure 25) for the earlier imaging time points. For imaging time

points 0-3s, non-musicians differed from musicians by activating more Heschl's gyrus (HG) on the right and a small region in the anterior part of the left planum temporale (immediately posterior to HG) when contrasts were corrected for multiple comparisons (Figure 26). Lowering the statistical threshold ($p < 0.001$, uncorrected) revealed additional activation of the right lateral cerebellum (lobulus V and VI) and the left hippocampal gyrus in the non-musician group (Figure 27).

9.4.3 Morphometric results

As previously shown (Steinmetz et al., 1991), PT measurements showed no significant difference for the left (t-value = 0.42), the right PT (t-value = -0.428), or the laterality index (t-value = -0.752) between musicians and non-musicians.

9.5. Discussion

Comparing the performance-matched non-musicians to the musicians revealed more right-sided activation of the planum temporale and the supramarginal gyrus (SMG) as well as bilateral activation of superior parietal areas. Lowering the statistical threshold led to additional activation of right inferior frontal and left supramarginal gyrus. Thus, both SMGs, to different degrees, were more activated in musicians compared to non-musicians. Recently, a positive correlation between the performance score in this particular pitch memory task and activation of the left supramarginal gyrus in a large group of non-musicians (Gaab et al., 2003a) was shown. It was argued, that better performing subjects used a more efficient short-term auditory storage region. The here presented study indicates that despite matching the two experimental groups in their performance scores, the musicians still show more activation of the SMG than the non-musicians. Several neurophysiological and lesion studies have shown the importance of the supramarginal gyrus for short-term auditory-verbal memory processes and phonological storage (e.g. Paulesu et al., 1993; Salmon et al, 1996). Previous studies (Celsis et al., 1999) extend the role of the SMG to a memory and storage center for non-verbal, musical information.

Interestingly, the musician group showed stronger activation of posterior superior temporal regions on the right, and SMG activation (right more than left) compared to the non-musician group. One possible explanation for this is that both groups showed a very strong left-sided activation with this task (see Figures 21, 22)

while the right hemisphere was activated to a lesser degree and showed more variability between the two groups. Thus, any voxel-by-voxel group differences would be more likely to show on the right hemisphere. Only by lowering the statistical threshold, additional differences in the left hemisphere, mainly in the left supramarginal gyrus (Figure 25) were seen, which again was more activated by the musicians than the non-musicians. Since none of the musicians had absolute pitch, these predominant right hemisphere group differences do not conflict with reports that have shown strong left-sided PT activations when musicians with AP were compared with musicians without AP (Ohnishi et al., 2001; Schlaug et al., 2001).

In addition to the activation of planum temporale and the supramarginal gyri, musicians also showed more right inferior frontal activation in contrast to the non-musicians, which appeared when the threshold was lowered. Zatorre et al. (1994) found profound right-sided inferior frontal lobe activations when comparing a pitch memory task with a passive listening task. The extensive and reciprocal fronto-temporal connections (e.g. Romanski et al., 2002; Petrides & Pandya, 1988) establish a fronto-temporal network that may be relevant for the temporal order or overall pattern of pitch-relevant information (Griffiths et al., 1999a). This confirms the findings of other studies showing activation of frontal brain regions when the analysis of higher order pitch patterns was required (Griffiths et al., 2001).

Furthermore, musicians showed more activation of the superior parietal lobe for the early time points as well as parts of the right superior parietal lobe for the later imaging time points. Several previous studies have shown the involvement of superior parietal areas in auditory tasks (Satoh et al., 2001). Some have argued that the parietal lobules are involved in auditory selective attention (Satoh et al., 2001), but it is also possible that musicians use a visual-spatial strategy and imagine the tones on a virtual staff in order to perform well in this pitch memory task (Platel et al., 1997; Sergent et al., 1992). Comparing the non-musicians with the musicians revealed bilateral activation of primary and early secondary auditory areas including Heschl's gyrus bilaterally and the anterior left planum temporale. Several studies have shown the importance of primary auditory areas for pitch discrimination (see review Tramo et al., 2002). In order to perform well in this task, non-musicians seem to rely more on a network that enables them to discriminate pitches.

In addition to differences between the two groups in perisylvian regions, differences in the left hippocampal gyrus were revealed. Neuroanatomically, the

auditory regions are closely located to the hippocampal region. Furthermore, an animal study showed that individual cells and cell assemblies in the hippocampus code memory processing of pitch and auditory temporal information in rats (Sakurai et al., 2002).

Non-musicians also showed more right hemispheric cerebellar activation. Several studies have now shown an involvement of the cerebellum in auditory tasks (for a short review see Gaab et al., 2003a), although the role of the cerebellum in pitch processing is not yet known. Possibilities range from facilitating pitch discrimination to sequential ordering of auditory information.

Overall, considering that both groups were matched in performance and did not show any significant brain asymmetries, the here presented results indicate perceptual and/or cognitive processing differences between musicians and non-musicians in this pitch memory task. Musicians activate a network that includes auditory short-term memory regions (e.g. SMG) and regions implicated in visual-spatial processing (e.g. superior parietal cortex). Non-musicians seem to rely more on a network that includes brain regions important for pitch discrimination (e.g. Heschl's gyrus) and traditional memory regions (e.g. hippocampal gyrus). Both processing strategies seem to lead to similar performance scores in this pitch memory task. Long-term musical training appears to influence the neural networks used for successful performance on this pitch memory task.

9.6 Short evaluation of specific aims for study C

Aim1: *Assessment of the functional anatomy of pitch memory in professional musicians*

In order to assess the effects that long-term training (often lifelong) has on brain activation patterns, several studies have focused on the highly specialized group of professional musicians. In this study, the neural correlates of the pitch memory task were revealed in a survey of a group of professional musicians. This group seemed to use brain regions specialized in short-term memory and recall in order to perform well in this pitch memory task.

Aim2: *Assessment of the functional differences between professional musicians and non musicians in performance matched groups.*

Functional differences between professional musicians and non-musicians have been revealed via various perceptual and cognitive tasks, including passive listening to music or performing pitch, harmony, melody, or rhythm tasks. Each of these studies either missed to assess behavioral correlates of the two groups or revealed significant differences between them. One can infer that these differences might be to the result of performance discrepancies between the two examined groups. Despite similar performance scores in the pitch memory task, results of this study illuminated differences in brain activation patterns. Since the performance scores of the two groups were matched, these results most likely reflect processing differences, which are possibly related to musical training, between groups.

10. STUDY D:

Developing musical expertise – the influence of training and musicianship

10.1 Specific aims for study D

Aim1: *Assessment of whether the activation pattern of non-musicians will change to a more musician like functional pattern after an one week auditory training.*

10.2 Introduction

Structural and functional differences comparing musicians with non-musicians have been found in perisylvian brain regions using morphometric (Schlaug et al., 1995a,b; Keenan et al., 2001; Schneider et al., 2002) and functional brain mapping techniques while subjects performed various auditory tasks (Mazziotta et al., 1982; Ohnishi et al., 2001; Besson et al., 1994; Platel et al., 1997).

The existing literature suggests that musical training modifies the laterality of activation pattern with more left-sided activation in musically trained subjects. However, most of these studies exhibited a performance difference between musicians and non-musicians in these musical tasks and it is possible that the difference in performance could also explain the group difference in lateralized activation.

Other possible explanations are that musicians use different cognitive strategies or have specialized musical abilities (e.g. absolute pitch) that could potentially account for between-group functional differences. In addition, anatomical differences may exist between musicians and non-musicians, likely due to intense and long-term auditory and motor training in musicians. These anatomical differences, if present, might also account for functional differences.

10.3 Materials and Methods

10.3.1 Subjects

In this study, seven non-musicians (three males and four females, age range) and fourteen musicians (eight females and six males) participated in the study after giving written consent. Both groups were part of earlier conducted pitch memory studies (see

Chapter 8 for non-musicians ["strong" learner] group and Chapter 9 for professional musician group). None of the non-musicians had any specific musical training or were trained in playing a musical instrument. However, some of them had received some musical instruction, usually as part of their regular high school education. The fourteen musicians were matched to the non-musicians in terms of gender and performance score in the given task. With regard to this experiment, musicians were defined as those who had a formal music education and played a musical instrument regularly. None of the subjects had any history of neurological or hearing impairment. All subjects were strongly right handed according to a standard handedness questionnaire (Annett, 1992).

10.3.2 Experimental tasks (Figure 9A)

The non-musicians were scanned twice separated by 7 days while performing a pitch memory task, which was contrasted with a motor control task. (for details see section 5.2)

All musicians were selected from a data pool and matched for gender and age and performance score in the pitch memory task. They underwent the scanning procedure only ones. The behavioral performance during the fMRI session was calculated as correct responses (in %).

10.3.3 Training

The training for the 7 non-musicians took place on the 5 consecutive between the two fMRI scanning sessions, starting with the following day after the first fMRI session (pre-training-fMRI) and ending the day prior to the last fMRI session (post-training-fMRI). Subject performed the above described pitch memory task for an hour with two short breaks in between. There was no training for the motor control task. While performing the task subject did not receive any feedback, although they got a feedback about their performance rate after each of the training session (see also section 8.3.3)

10.3.4 FMRI design and parameters

The fMRI design and the modified sparse temporal sampling method (described in detail in section 6.1) was applied in each scanning session (two for non-musicians separated by a week, one for the professional musicians)

10.3.5 FMRI data analysis

FMRI data were analyzed using the SPM99 software package (Institute of Neurology, London, UK). Each set of axial images for each subject was realigned to the first image, co-registered with the corresponding T1-weighted data set, spatially normalized to the SPM99 template using a non-linear spatial transformation with 7x8x7 basis functions, and smoothed with an isotropic Gaussian kernel (12mm full-width-at-half-maximum). Condition and subjects effects were estimated using a general linear model (Friston et al., 1995a,b). The effect of global differences in scan intensity was removed by scaling each scan in proportion to its global intensity. Low frequency drifts were removed using a temporal high-pass filter with a cutoff of 200s. Because of the sparse temporal sampling design there is no temporal auto-correlation between the images. Therefore, the data was not convolved with the hemodynamic response function (HRF) and a low-pass filter was not applied.

10.4 Results

10.4.1 Behavioral results:

In the initially test (before the training), the non-musicians showed a performance score of 69.57% (SD = 7.27). After the one week training the mean performance score in this group increased significantly to 84.57% (SD = 3.72). The mean performance score for the musicians was 80.14% (SD = 7.18).

There was a significant difference for the behavioral results for the musicians and the pre training non-musicians ($T=3.165$, $p< 0.005$). After the training, both groups showed no longer a significantly difference.

10.4.2 FMRI results

Figure 28 shows the mean activation for (A) the non-musicians prior to the training, (B) the musicians without training and (C) the non-musicians after the training.

10.4.2.1 Comparing musicians and pre-training non-musicians

In comparison to the non-musicians before the training, musicians showed more activation of the left supramarginal gyrus (-50/-36/21, FDR-corrected, Figure 31, 32). By contrasting the pre training scans of the non-musicians with the musicians, revealed more left sided activation of the Heschl's gyrus (-52/-29/7) for the non-

musicians ($p < 0.05$; FDR-corrected, Figure 29). When raising the threshold, activation of the right superior temporal sulcus, the right inferior frontal lobe (48/14/16 and 47/16/20) and the left parahippocampal gyrus (-18/-19/-14; Brodmann 35) were revealed (Figure 30).

10.4.2.2 Comparing musicians and post-training non-musicians

The trained non-musicians, in comparison to the musicians, showed more left hemispheric primary and secondary auditory activation (-51/-26/ 8) for $p < 0.05$, FDR-corrected (Figure 33). Lowering the threshold to $p < 0.001$ (uncorrected) revealed additionally right hemispheric cerebellar activation (18/-32/-12 and 25/-59/-21) as well as activation of the cuneus (-1/-94/4) and the fusiform gyrus (-32/-77/-15). Furthermore, the musicians showed more activation of the right superior parietal lobule (33/-54/50; Brodmann 7) and the left inferior parietal lobule (-45/-58/-32) when applying an uncorrected threshold of $p < 0.001$ (Figure 34).

10.5 Discussion

Musicians had more activation of the left supramarginal gyrus (SMG) than the non-musicians (prior to pitch memory training). A larger group analysis showed recently that the supramarginal gyrus activation is positively correlated with good performance in a pitch memory task (Gaab et al., 2003a). Several neurophysiological and lesion studies revealed the importance of the SMG - particularly on the left - for short-term auditory-verbal memory processes and phonological storage (e.g., Salmon et al., 1996; Paulesu et al., 1993; Celsis et al., 1999). The increased activation of the SMG found in the better performing non-musicians (Gaab et al., 2003a) as well as in professional musicians indicates that these individuals are activating a brain region that might be particularly suited for short-term memory processes of verbal and non-verbal information.

Contrary to that, the untrained non-musicians had more activation of primary auditory cortex than trained musicians. Primary auditory cortex has been found to be important in pitch discrimination tasks (Tramo et al., 2002). Thus, the difference in the activation pattern might indicate a difference in strategy as well as a difference in performance. Musicians might rely more on a region particularly suited for short-term auditory memory. They might try to memorize the first tone for a comparison with the

last or second-to-last tone. The non-musicians might try to continuously discriminate between tones without effectively storing the first tone in memory.

After a week of training in the pitch memory task, non-musicians now showed more activation of primary and secondary auditory areas on the left in comparison to the musicians. Several studies have shown a left more than right hemispheric processing depending on musical expertise (Kimura et al., 1964; Johnson et al., 1977; Bever & Chiarello, 1974; Mazziotta et al., 1982; Hassler, 1990; Messerli et al., 1995; Evers et. al., 1999; Ohnishi et al., 2001). The here presented data would support the notion that training non-musicians in a musical task can lead to a change in the hemispheric activation pattern.

Musicians in comparison to the group of trained non-musicians showed more activation of the superior parietal lobule on both sides. This finding is consistent with previous studies in other domains showing a decrease in activation in parietal associative cortex either after training or as a result of practice (Kassubek et al., 2001; Jenkins et al., 1994; Petersen et al., 1998; Pardo et al., 1991). Those studies interpreted their results with e.g. habituation in the course of increased familiarity with the general conditions, reduced arousal, an automaticity i.e. decreased dependence on attentional and working memory resources as a consequence of practice. Interestingly, after the training of the non-musicians, there was no more significant difference between the two groups in the supramarginal gyrus. Therefore, one can interpret, that the non-musicians changed their brain activation pattern towards a more musician like processing pattern after the training. The performance score indicate, that this strategy is more efficient and leads to no more behavioral differences between the groups. As mentioned before, the supramarginal gyrus seem to play a key role in efficiently performing this pitch memory task and the here presented study shows that a one week training can lead to activation of a more efficient network. Nevertheless, there were still significant differences between the two groups. It seems, that the non-musicians need to rely more on primary and secondary auditory areas in addition to the supramarginal gyrus in order to reach the same performance score than the professional musicians.

10.6 Short evaluation of specific aims for study D

Aim1: *Assessment of whether the activation pattern of non-musicians will change to a more musician like functional pattern after an one week auditory training.*

In conclusion, this study provides evidence that auditory training can trigger changes in the functional network, subserving a pitch memory task. The activation pattern of trained non-musicians becomes more lateralized on the left side and shows less activation of parietal and inferior frontal brain regions. Nevertheless, non-musicians rely more on primary and secondary auditory areas in order to achieve the same performance score. Thus, the differences between musicians and non-musicians might be related to training.

11. Study E:

The influence of gender on the neural correlates of pitch memory

11.1 Specific aims for study E

Aim1: *Assessment of gender differences in the brain activation pattern in the developed pitch memory task*

11.2 Introduction

Anatomical differences have been reported between the genders in regions that are classically associated with language processing, with the majority of studies indicating that females may be less lateralized than males (Amunts et al., 1999; Kulynych et al., 1994; Shapleske et al., 1999; Good et al., 2001a), though the significance and magnitude of these anatomical differences is disputed (Jancke et al., 1994; Foundas et al., 1999).

These anatomical differences may lead to divergences in cognitive processing between the genders, such that females may employ a less lateralized processing than males (Coney, 2002; McGlone, 1980; Voyer, 1996). This idea has been examined in terms of actual brain/behavior relationships between the genders. While some functional brain mapping studies and behavioral studies have indicated that there are laterality differences (Coney, 2002; Shaywitz et al., 1995; Boucher & Bryden, 1997; Walla et al., 2001), there is also conflicting evidence as well (Frost et al., 1999; Kertesz & Benke, 1989; Speck et al., 2000) indicating that both genders activate similar brain regions in language processing. Complicating the situation even further, there is one study indicating that females may be more lateralized than males (Obleser et al., 2001).

Several studies have indicated that there is sharing in the neural substrates between language and music (Besson & Schon, 2001; Maess et al., 2001). Therefore, the observed anatomical asymmetry in auditory related regions should have the same implication for language (Foundas et al., 1994; Good et al., 2001a; Kulynych et al., 1994; Steinmetz et al., 1991) as well as for music processing (Schlaug et al., 1995a,b; Keenan et al., 2001). Furthermore, the lesser anatomical asymmetry of females (as indicated in some studies) indicates that gender might have an influence not only on

language processing but also on music processing. However, in terms of the potential impact of gender on brain differences in the processing of musical information, there have been only a few behavioral studies (Hough et al., 1994) and no functional imaging study. This is surprising given the hypothesized importance of musical processing in terms of language development, human communication, brain development and evolution (Besson & Schon, 2001; Gray et al., 2001), as well as the speculation that both musical and language processing occupy similar (Besson & Schon, 2001; Maess et al., 2001; Peretz et al., 2002) or distinct (Erdonmez & Morley, 1981; McFarland & Fortin, 1982) neural substrates. In terms of musical processing, functional and anatomical differences depend on a variety of variables among them handedness, musicianship, and exceptional abilities such as absolute pitch (Keenan et al., 2001; Ohnishi et al., 2001; Pantev et al., 2001; Patel & Balaban, 2001; Zatorre, 1985, 1998; Zatorre et al., 1998); the effects of gender on music processing is relatively unexplored compared to studies done on the interaction between gender and language processing.

In this study, the aim was to examine whether pitch processing would show similar hemispheric gender differences as has been reported for language processing. In particular, the goal was to examine whether anterior (e.g., frontal opercular) and posterior (e.g., superior temporal gyrus) perisylvian differences between males and females could be revealed. By employing a sparse temporal fMRI technique (Hall et al., 1999, 2000; Bandettini et al., 1998; Edmister et al., 1999) with a jitter-like acquisition, an auditory activation pattern without interferences from the MR scanner noise could be obtained

11.3 Material and Methods

11.3.1 Subjects

Eighteen right-handed volunteers (age range: 18-40; nine females and nine males) participated in the study after giving written informed consent according to institutional guidelines. Some of the subjects in this study were also part of a different analysis on the time course of the activation pattern and on the relationships between performance and activity changes (Gaab et al., 20003a). None of the participants in this study had any specific musical training or were trained in playing a musical instrument. However, most of them had received some musical instruction, usually as

part of their regular high school education. None of the participants had any history of neurological or hearing impairment. All participants were strongly right handed according to a standard handedness questionnaire (Annett, 1992).

11.3.2 Experimental task (Figure 9A)

All participants performed a pitch memory task contrasted with a motor control task (for details see section 5.2). All participants performed above chance in the pre-scanning testing phase.

11.3.3 FMRI design and parameters

The fMRI design and the modified sparse temporal sampling method (described in detain in section 6.1) was applied

11.3.4 FMRI data analysis

Data were analyzed using the SPM99 software package (SPM99, http://www.fil.ion.ucl.ac.uk/spm, Wellcome Department of Cognitive Neurology, London, UK). Each set of axial images for each subject was realigned to the first image, co-registered with the corresponding T1-weighted data set, spatially normalized to the SPM99 template using a non-linear spatial transformation with 7x8x7 basis functions, and smoothed with an isotropic Gaussian kernel (8mm full-width-at-half-maximum). Condition and subject effects were estimated according to the general linear model at each voxel in brain space (Friston et al., 1995a,b). The effect of global differences in scan intensity was removed by scaling each scan in proportion to its global intensity. Low frequency drifts were removed using a temporal high-pass filter with a cutoff of 200s. The data was not convolved with the hemodynamic response function (HRF) and a low-pass filter was not applied. Furthermore, a box-car function with an epoch length of 1 to the fMRI time series (47 acquisitions within each of the two runs) was applied. No temporal derivatives were applied.

Significantly activated brain regions were determined by contrasting pitch memory to the motor control task for all 7 imaging time points separately. Initially, all 7 imaging time points were explored separately to determine whether or not there was a trend in the activation pattern over time. For the main analysis of the data, the first to the fourth imaging time point (0-3s after the end of the auditory stimulation) and

the fifth to the seventh imaging time points were combined (4-6s after the end of the auditory stimulation) into two blocks in order to (1) to achieve a higher number of events or acquisitions per block for statistical reasons, and (2) to reflect the main change over time in the activation pattern, since the initial imaging time points reflected more a perception network while the later time points reflected more a memory network. In the fMRI-analysis the pitch memory task was contrasted with the motor control task for these two combined clusters of imaging time points. Linear contrasts were used to test hypotheses regarding regionally specific condition effects, which produced statistical parametric maps of the t statistics generated for each voxel (SPM {t}).

Between group differences were determined by examining the interaction between gender and task activations by contrasting the two groups (males and females) for the task-specific activations. Voxels were identified as significant ($p<.05_{adj}$) only if they passed a height threshold of $p< 0.05$, corrected for multiple comparisons, and belonged to a cluster of activation with an extent of at least 12 voxels (k = 12; number of expected voxels per cluster). Data are also presented derived from a $p<.001$ threshold ($p<.001_{ucor}$) which was not corrected for whole brain space, but all activations discussed in this report were significant after a small volume correction was applied with a spherical ROI with a radius of 25 mm, centered at the local maximum, for the inferior frontal gyrus, the superior temporal gyrus, and the cerebellum. This analysis was done in order to examine whether regions (in addition to the superior temporal gyrus) previously shown to exhibit gender-related anatomical differences in some studies (e.g., frontal operculum) would also show functional differences in this pitch memory study. These observations may generate further hypotheses and their significance can be tested in future studies. Both, the left frontal opercular and right cerebellar activation were significant when a small volume correction was applied.

11.4.Results

11.4.1 Behavioral results

There were no significant differences in the behavioral performance between both genders ($p > .05$).

11.4.2 FMRI results

During the early "perceptual" phase of the here presented task (ITP 0-3s after the end of the auditory stimulus), the overall group analysis for the contrast pitch memory versus motor control revealed bilateral (more left than right) superior temporal gyrus (including primary and secondary auditory areas) as well as bilateral supramarginal gyrus, bilateral superior parietal lobe (right more than left), bilateral dorsolateral posterior frontal, and bilateral cerebellar (more left than right) activations (Figure 35A). In this early imaging phase ("perceptual" phase) males differed from females (Figure 35C and 35E, Figure 36A and 36B) by activating predominantly the left superior temporal gyrus (Talairach coordinates: -55.3, -24.6, 3.6) ($p< 0.05$ FDR corrected) in addition to a small activation of the right superior temporal gyrus (Talairach coordinates: 53.7, -11.1, -2.8) (Figure 36A). Adjusting the significance threshold ($p< 0.001$ uncorrected) to examine further the pre-specified hypothesis, additional differences in the anterior and posterior superior temporal gyrus and the left frontal opercular region were found (Figure 36B). The only other difference that emerged at that statistical threshold was a greater right cerebellar activation (lobules V and VI) in males compared to females. These activations were deemed significant and adjusted for multiple comparisons if a small volume correction using a sphere with a radius of 25 mm, centered on the local maximum, was applied that included the inferior frontal gyrus, the superior temporal gyrus, and the cerebellum. At this lower threshold, an additional greater activation of the left posterior dorsolateral frontal cortex in males compared to females emerged as well.

During the later imaging time points ("memory" phase) of the task (ITP 4-6s after the end of the auditory stimulation), the overall group analysis for the contrast pitch memory versus motor control task showed activations of secondary posterior auditory areas bilaterally, superior parietal lobe (right more than left), temporal pole as well as cerebellar regions (lobule V and VI) bilaterally. In addition, there was activation of the posterior dorsolateral frontal cortex as well as the inferior frontal gyrus on the left (Figure 35B).

During these later imaging time points (ITP 4-6s), males did not exhibit any strong significant differences from females (Figure 35D and 35F). However, when the significance threshold was lowered ($p< 0.001$uncorrected), differences were found in the right cerebellum again.

Females did not show any significant activation differences compared to males in the early, "perceptual" phase (ITP 0-3s) of the pitch memory task. During the "memory" phase (ITP 4-6s), females differed from males by showing activation of the posterior cingulate/retrosplenial region ($p < 0.05$ FDR corrected) (Figure 37). Females in comparison to males did not demonstrate significant activation in either left or right inferior frontal or superior temporal brain regions at any of the imaging time points (Figure 37).

11.5 Discussion

These data confirm a number of theories regarding cognitive processing differences between the genders. Specifically, in this pitch memory task, males showed more lateralized temporal lobe activation during the early, "perceptual" phase compared to females, indicating that females are more symmetric and males more asymmetric in their activation pattern. This was further supported by finding more left hemisphere activation in the frontal opercular and posterior perisylvian activation in males compared to females when the strong statistical threshold was lowered. These activations were significant when a small volume correction was applied. The most pronounced and statistically strongest differences were seen in the left superior posterior temporal gyrus, a region commonly referred to as planum temporale. Anatomical differences have been reported between the genders in this region with the majority of studies indicating that females may be less lateralized (Kulynych et al., 1994; Shapleske et al., 1999; Good et al., 2001a). The here presented data adds functional significance to this anatomical trend using a pitch memory experiment. An MEG study examining early cortical responses to pure tones, found a similar left hemisphere advantage in males compared to females, although native language modulated the degree of laterality in this study (Salmelin et al., 1999).

Based on previous studies on a variety of cognitive tasks (Johnson & Kozma, 1977; McGlone, 1980; Voyer, 1996), including musical performance (Davidson et al., 1976), as well as anatomical examinations of the corpus callosum (DeLacoste-Utamsing & Holloway, 1982; Holloway & de Lacoste, 1986; Johnson et al., 1994; Oka et al., 1999; Steinmetz et al., 1995), it has been speculated that females might have a less lateralized strategy in processing auditory information due to their higher

interhemispheric connectivity based on their relative callosal size differences (Filipek et al., 1994; Jancke et al., 1994; Preis et al., 1999; Steinmetz, 1996).

An interesting aspect of the here presented results are that males had more cerebellar activations compared to females with regard to this pitch memory task. Over the last years, the cerebellum has been found to play a role in multiple musical perceptual tasks (Griffiths et al., 1999a; Hugdahl et al., 1999; Perry et al., 1999; Riecker et al., 2000; Satoh et al., 2001), as well as rhythmic processing (Penhune et al., 1998). However, the role of gender in musical processing in the cerebellum has remained unexplored. Males having a greater right cerebellar activation (possibly connected to a greater left lateralized activation in the perisylvian region not seen in females), indicates a greater lateralized processing strategy. Recent anatomical data (Schlaug, 2001) also indicate possible structural gender interactions in the cerebellum with male musicians significantly differing in cerebellar volume compared to male non-musicians, while no such structural difference was seen comparing female musicians with female non-musicians.

The stronger activation of the left frontal operculum (Broca's region) in males compared to females is intriguing considering some of the recent findings that implicate this region in music processing (Maess et al., 2001) in addition to it's role in language processing. While there may be gender differences in the structure of Broca's regions (Amunts et al., 1999), not all functional studies using various language paradigms agree on gender differences in either anterior or posterior perisylvian regions. Frost and colleagues (Frost et al., 1999), testing 50 males and females, found a left lateralized activation in a language comprehension task without any significant gender differences. This differs from a study by Shaywitz et al. (1995) in which a leftward lateralization in the inferior frontal region was found in a phonological task in males while the female activation pattern was more diffuse involving both left and right inferior frontal gyrus. In terms of music processing, Broca's region has been implicated in rhythmic processing (Platel et al., 1997) as well as the analysis of music harmony (Maess et al., 2001; including Broca's right homologue). The current data may indicate that gender differences may influence musical processing in terms of Broca's region. The relation between these gender differences and the underlying anatomy is not known.

At the lower statistical threshold, an activation within the left dorsolateral frontal lobe could be observed. Although, there was no *a priori* hypothesis for gender

related functional differences in this region, activation in the region has been described when musicians with and without absolute pitch had to make an explicit judgment whether an interval was a minor or major third or when AP musicians passively listened to the same tone pairs (Zatorre et al., 1998). It was thought that this region was activated when a verbal label was associated with a pitch or an interval identification. In the here presented study, males activated this region more than females. Future studies will have to determine the role of this region in gender interactions with a variety of auditory tasks.

A bihemispheric pattern of activation, which was more left-lateralized in males compared to females, could be observed. The bi-hemispheric activation across the entire group as well as the left more than right lateralization in activation in males is different compared to some other studies finding a more right-ward activation pattern in a mixed gender group (Zatorre et al., 1994) using a similar task but different control conditions. The issue of right more than left and left more than right activations in pitch tasks or more general in musical tasks is unsolved. There are almost an equal number of papers reporting a left-lateralization of the activation pattern than there are papers reporting a right-lateralization of the activation pattern (Zatorre et al., 1994; Griffiths et al., 1997; Platel et al., 1997; Celsis et al., 1999; Salmelin et al., 1999; Clarke et al., 2000). Across all studies, a bihemispheric activation pattern is most commonly found. This is the here revealed finding as well (Figure 35A-F), although gender seems to affect the lateralization of activation similar to what is reported in language studies. It cannot completely rule out that the here examined subjects used some sort of verbal code to solve the pitch memory task, although none of them reported doing this and none of the subjects had absolute pitch. It is also unlikely that the visual prompt shown at the end of the auditory stimulation could have caused the more left-than-right activation in the male subgroup, since the inherent cerebrovascular delay in response to a visually presented verbal command would have caused a left temporal lobe activation at the last imaging time points, but this was not seen.

Although the distinction between a “perceptual” phase (early imaging time points) and a “memory” phase is arbitrary, the activation maps (Figure 35 and 36) as well as the regional data (Table 3) support a distinction into two phases. Zatorre et al. (1994) argued that a distinction between a more perceptual analysis mechanism involving primarily temporal cortex (including primary auditory cortex) and an

auditory working memory mechanism involving complex temporo-frontal interactions can be made in pitch memory tasks. The decision to distinguish between a more perceptually-weighted initial phase and a more memory-weighted later phase is based on these observations. As can be seen in Figure 35 as well as in the more detailed region of interest analysis (Table 3), the activation patterns for temporal and non-temporal regions differed between the early and late imaging time points. Initially, there was strong primary auditory cortex activation, which was later followed by more prominent activation of secondary auditory areas as well as other frontal and parietal brain areas.

Females differed from males by having more bilateral activation of the posterior cingulate/retrosplenial cortex. This region has been implicated recently in memory tasks when the familiarity of faces or voices needed to be judged (Shah et al., 2001). Furthermore, the retrosplenial cortex has been implicated in episodic memory retrieval and emotional salience (Valenstein et al., 1987). Therefore, the gender differences in brain activation may provide evidence for strategic processing differences for the memory component of the here developed pitch memory task.

In summary, the processing of this pitch memory task revealed a more left than right lateralized processing during the early "receptive" phase in males compared to females. Activations were seen in regions with gender related structural brain differences according to several reports such as the superior temporal gyrus, the frontal operculum, and the cerebellum, although the degree and the magnitude of these differences are still disputed among several studies. Females showed more activation than males in the posterior cingulate/retrosplenial region, possibly indicating a gender difference in the memory component of the here used task. Since both groups did not differ in their performance and since performance differences can therefore not explain the activation differences, the here observed gender differences might indicate a difference in perception or strategy in solving the pitch memory task.

11.6 Short Evaluation of specific aims for study E

Aim1: *Assessment of gender differences in the brain activation pattern in the developed pitch memory task*

Various studies showed differences in brain activation pattern between females and males. In general females show a less lateralized brain pattern for various task

including language tasks. This study supports the previous findings showing less lateralized processing for the given pitch memory task, whereas males process the pitch memory task more in the left than the right hemisphere.

12. Study F:

The influence of sleep on auditory learning – a behavioral study

12. 1 Specific aims for Study F

Aim 1: *Assessment of whether auditory learning is time-, practice- or sleep-dependent.*

Aim2: *Assessment of the effects of sleep quality and sleep duration on auditory learning*

12.2 Introduction

In 1970, Lucero first demonstrated an increase in rapid eye movements (REM) sleep in response to a maze learning experiment in rats (Lucero, 1970). Since then, a large number of studies have shown the influence of sleep on learning, and concomitantly, the influence of learning on subsequent sleep augmentation (for reviews see Smith, 1995; Peigneux et al., 2001; Siegel, 2001). More specifically, several studies in humans have reported that sleep may be especially important for the consolidation of procedural skill learning in the visual (Karni et al., 1994; Stickgold et al., 2000a,b; Gais et al., 2000) and motor (Walker et al., 2002, 2003a,b; Fischer et al., 2002) domains. However, there has been a lack of studies assessing the direct influence of sleep on auditory learning in humans.

Several studies have investigated the influence of auditory stimulation on sleep architecture. For example, (Cantero et al., 2002a,b) have shown changes in EEG characteristics during human slow-wave sleep after 6 hours of continuous auditory stimulation during previous wakefulness. Synaptic reorganization during sleep after prolonged exposure to a novel sensory experience was hypothesized to underlie this observation. Mandai and colleagues (Mandai et al., 1989) have shown that Morse code learning can lead to an increase of REM sleep and number of REM episodes, with a correlation between performance and rapid eye movement activity. There is also evidence that learning of a complex logic task while hearing a clicking sound in the background during wakefulness can be modified by presenting the same auditory cues during REM sleep periods leading to improved performance if tested one week

later in comparison to a group with no auditory REM sleep stimulation (Smith & Weeden, 1990).

Despite these findings, few studies have assessed the differential contribution of time periods containing wake or sleep on the consolidation and delayed learning of auditory skills. In the current study, the previously developed auditory pitch memory task was used with the aim to differentiate between the effects of time periods containing either wake or sleep on subsequent delayed learning of this task, following initial training.

12.3 Materials and Methods

12.3.1 Subjects

Fifty-six normal right-handed volunteers (age range: 18-40 (mean: 26.5; SD: 4.7); thirty-five females and twenty-one males) participated in the study after giving written informed consent. Because a previous study examined a musicianship effect on this task, only non-musicians were included in this study (Gaab et al. 2003b). One subject had to be excluded from the final analysis because he had only slept two hours before the retesting. Subjects were unselected for musical training; most had received some musical theory classes, usually as part of their elementary, high school, or college education, but none were professional musicians and none of the subjects actively played any instruments. No subject had a history of any hearing impairments, psychiatric or neurological disease, nor were they under the influence of any hypnotic, anti-allergic, sedative or anti-depressant medications. Subjects were not allowed to consume coffee or tea during the 24 hours prior to the experiment or during the experiment. All subjects were strongly right handed according to a standard handedness questionnaire. Subjects were randomly assigned to either the morning or evening group (28 subjects in the morning group and 28 in the evening group).

12.3.2 Experimental task

All subjects performed the pitch memory task (for details see section 5.2 and section 12.3.3 below) in front of a computer screen with headphones. There was no motor control task in this experiment.

12.3.3 Experimental paradigm (Figure 38)

All subjects underwent three sessions (S1-S3). Each session consisted of two testing trials (referred to as first testing and second testing) and two training trials separated by a short break in between the testing trials (Figure 38). Each testing and training trial lasted 8 minutes. During the training trials, subjects received visual feedback indicating whether the answer they provided were a correct or incorrect.

Subjects in this morning group (MG) underwent their initial session (S1) at 9 a.m. (+/- 1hr), which was followed by two more sessions, the first one 12 hours later (period of wakefulness) and the second one 24 hours later after a night of sleep.

Subjects in this evening group (EG) underwent their initial session at 9 p.m. (+/- 1hr) followed by a session 12 hours later (after a night of sleep) and a second session 24 hours later after a period of wakefulness.

All subjects filled out a sleep log to detail the amount of sleep during the night before the initial test and the night within the experimental sessions and to screen for possible sleep disorders and medication use. Furthermore, at each testing point, all subjects completed the Stanford Sleepiness Scale (SSS), a standard measure of subjective alertness (Hoddes et al. 1973). The behavioral performance for each testing and training trial was calculated as correct responses (in %) of all responses. None of the subjects missed more than 4 trials per session.

The statistical analyses were performed using paired t-tests and repeated measurement ANOVAs across groups. Dependent variables were % correct responses in % between sessions, amount of sleep, and Stanford Sleepiness Scale (SSS) scores. The first analyses tested (repeated measurement ANOVAs) whether or not there is any performance difference between the two groups in their initial session and for each of the groups within subsequent sessions to exclude possible diurnal effects on delayed sleep dependent learning. A repeated measurement ANOVA was performed for the initial session and each of the two subsequent sessions with group as a factor (MG and EG) and four % correct responses as dependent variable. All ANOVAs have been tested in regards to the assumption of equal variances. No violation of this assumption could be found. The next analyses tested whether or not both groups combined and separated showed a significant delayed learning effect only after sleep, but not across equivalent periods of wake, regardless of which came first.

12.4. Results

12.4.1 Effects within the initial session (session 1)

Across both groups, there was significant performance improvement comparing % correct responses in testing 1 with testing 2 of the initial session using a repeated measurement ANOVA ($F = 11.683$, $df = 1$, $p = 0.001$; $\varepsilon^2 = 0.178$). Furthermore, performance (i.e., % correct responses) was not different across this initial session (two testing and two training trials) when comparing the two groups ($F = 1.399$, $df = 3$, $p = 0.245$; $\varepsilon^2 = 0.026$). Indeed subjects achieved almost identical performance levels by the end of this initial session with a mean performance difference of 1.8%. Thus, performance improved significantly within the first (initial) session for morning and evening groups equally, despite the differing circadian time points.

12.4.2 Effects in the morning group (Figure 39)

The MG showed only a non-significant improvement (1.6%) from the last testing trial of session 1 to the first testing trial of session 2 which were separated by 12 hr of wakefulness ($t = 0.335$, $p = 0.740$). However, when retested a second time after an additional 12 hrs containing a night of sleep, the MG group showed an 11.77% increase in their performance (t (one-tailed) $= 3.538$, $p < 0.000$).

12.4.3 Effects in the evening group (Figure 40)

While it was clear from the MG that a delayed improvement on this task was occurring during the second 12hrs containing sleep, these data alone could not determine whether sleep was the primary factor, or whether the delayed learning simply required more than 12hrs before becoming evident. Subjects in the EG addressed this issue. They were initially tested in the evening and showed a significant improvement of 5.7% when retested after just 12hrs (t (one-tailed) $= 1.714$ $p < 0.05$) containing a night of sleep However, when retested again 12hrs later (total of 24hrs after initial session) containing a period of wakefulness, there was no further change in performance level ($t = 1.450$; $p = 0.159$).

12.4.4. Sleep and wake effects across groups

In order to test for an effect of delayed learning following sleep in comparison to learning following wakefulness we applied a t-test with the improvement in %

following sleep and following wakefulness in both groups as variables. This analysis revealed a significant difference for delayed learning following sleep ($t = 3.173$; $p < 0.005$).

12.4.5 Learning within retest sessions

Neither the morning nor the evening group showed a significant change in their performance within each of the retest sessions (morning group: session2, $F = 0.708$; $df = 3$ $p > 0.05$; $\varepsilon^2 = 0.026$; session3, $F = 0.732$; $df = 3$ $p > 0.05$; $\varepsilon^2 = 0.027$; evening group: session2, $F = 0.195$; $df = 3$ $p > 0.05$; $\varepsilon^2 = 0.007$; session3, $F = 1.744$; $df = 3$ $p > 0.05$; $\varepsilon^2 = 0.063$). Thus, there was no evidence of subsequent within session learning either in the morning or the evening group.

12.4.6 Sleep quality and alertness

A repeated measurement ANOVA did not reveal any significant difference in the Stanford Sleepiness Scale (SSS) ratings of alertness within any of the groups (MG : $F= 0.857$, $df=2$, $p=0.430$, $\varepsilon^2 = 0.031$; EG: $F= 1.203$, $df= 2$, $p= 0.309$, $\varepsilon^2 = 0.046$) or across groups for the three sessions ($F = 0.786$, $df = 2$, $p = 0.458$, $\varepsilon^2 = 0.024$). On the 7-point scale (1 being most alert), mean values for all sessions were 2.265 (MG) and 2.20 (EG). There were no differences in the SSS ratings between sessions for either group as well as between groups. Furthermore, there was no significant correlation with retest performance scores and alertness ratings either for the morning group ($r = 0.089$; $p= 0.517$) or the evening group ($r =0.079$; $p =0.567$).

Based on the documented sleep logs, subjects in the MG and EG did not differ in the amount of sleep across each experimental night ($t =1.691$; $p =0.097$). Group averages were 7.63 hrs (SD = 0.77) for the morning group and 8.00 hrs (SD = 0.86) for the evening group.

12.5. Discussion

This study investigated the effects of time in general, time awake and time containing sleep on the consolidation and delayed learning of an auditory pitch memory task. The results demonstrate that, additional learning takes place in the absence of further practice, following an initial training induced performance improvement. However, the delayed learning occurred exclusively across time periods containing sleep, and

not across equivalent time periods of daytime wakefulness, regardless of whether the time awake or time asleep came first.

This study cannot completely rule out circadian factors that may have prevented the expression of learning after 12hrs of wake. However, this explanation is unlikely for several reasons. Firstly, learning across the initial training session was similar for both groups of subjects, regardless of whether they were trained at 9 a.m. or 9 p.m. Secondly, there was consistently no further practice-dependent, within session learning, at each subsequent retest session for either group, either in the morning or evening. Thirdly, there were no significant differences between subjective alertness ratings either in the morning or evening, and no correlation was found between these measures and task performance. Thus, on can consider sleep itself to be the most reasonable source of the delayed improvement on this task.

The here presented findings support previous studies indicating an interaction between auditory learning and sleep (Cantero, 2002a,b; Mandai et al., 1989; Smith & Weeden 1990; Atienza et al., 2003). While these studies have demonstrated either alterations in sleep architecture following a prior waking experience, or changes in the electrical evoked response after sleep, the here described studies reports the description of improved behavioral performance following sleep on an auditory skill task. This data are consistent with evidence of sleep-dependent learning in studies probing both visual and motor skill domains (Karni et al., 1994; Stickgold et al., 2000a,b; Gais et al., 2000; Walker et al., 2002,2003a,b; Fischer et al., 2002). Several of these studies have specifically highlighted particular types of sleep at certain times of the night as being important for the consolidation process. In the current study, sleep in the sleep lab using polysomnography was not recorded, and it therefore remains an open question as to whether this overnight improvement is sleep, sleep-stage, or sleep-stage window specific.

The current behavioral study did not assess the specific neural correlates of this sleep-dependent auditory learning, but functional imaging changes in secondary auditory-related brain regions within the posterior superior temporal gyrus and the inferior parietal cortex have been previously reported after 7 days of intensive training on this task in subjects who showed a strong learning effect. Those subjects that did demonstrate only a weak learning effect showed functional imaging changes in the lingual, inferior frontal and parahippocampal gyrus (see chapter 8). One possible hypothesis is that the sleep-dependent behavioral improvements observed in this

study, may in part, be related to an overnight consolidation or reorganization in early cortical processing regions, together with decreasing activity in brain regions associated with attention and working memory leading to improved efficiency of stimulus processing.

12.6 Short evaluation of specific aims for study F

Aim1: *Assessment of whether auditory learning is time-, practice- or sleep dependent.*

Various studies have shown the integral role that sleep plays in visual and motor skill learning, but the influence of sleep on auditory learning has not been explored to date. By carefully designing the experimental set up and assessing two groups, one was able to distinguish between time-, practice- and sleep-dependent learning. Both groups improved significantly only after sleep, and not across time periods of wake, Regardless of whether the sleep period or the wakefulness period occurred first, the performance of both groups improved significantly only after sleep and not across time periods of wakefulness, indicating the important role that sleep may play in the consolidation of an auditory skill memory task.

Aim2: *Assessment of the effects of sleep quality and sleep duration on auditory learning*

Several previous studies revealed correlations between sleep duration, sleep quality and learning in various domains. This study, however, could not reveal such correlations. However, subjects in this study were asked to keep their usual sleeping duration throughout the experiment. One can argue, that a constant individual sleep duration, rather than the sleep duration per se, may play an important in assessing the influence of sleep on auditory learning. In addition, all subjects in this study reported good sleep quality scores for the one night they slept during their experimental session. Therefore, there was only a small variability among the sleep quality scores within and between the two groups. This could be one reason for the missing correlation between sleep quality and auditory learning, Further studies, varying sleep duration (e.g. sleep deprivation) and sleep quality are needed in order to clarify this hypothesis.

III GENERAL DISCUSSION

This body of research could reveal important findings regarding the time course and the functional anatomy of pitch perception and pitch memory, training –induced functional changes following a pitch memory training, as well as the influence of musicianship, gender and sleep on pitch memory processing and auditory learning. Furthermore, most of the here presented studies demonstrate the need to include performance scores in analyses of functional imaging data.

The following chapter will primarily offer a short evaluation of this project's general aims, which were outlined in chapter 4. Additionally, the role of the SMG (section 14.1) and the cerebellum (section 14.2) in auditory processing will be discussed in further detail. Furthermore, the here presented data from the auditory domain will be integrated into the "scaffolding-storage" framework by Petersen et al. (1998).

13. Short evaluation of the general aims

This chapter will briefly evaluate each of the general aims outlined in chapter 4.

General aim 1: *Development of an auditory task, which contains a perceptual and a memory component.*

Over time, the developed task (see section 5.2) showed a distributed and dynamic network activation pattern, which could be divided into a perceptual and a memory component (StudyA), according to the observed imaging pattern and the underlying literature regarding pitch perception and perceptual auditory processing. The early imaging time points (ITPs) revealed involvement of primary and secondary auditory areas (perceptual phase) which were followed by activation of the supramarginal gyrus, posterior dorsolateral and inferior frontal regions as well as superior parietal regions for the later ITPs (memory phase). In addition to this, a region of interest analysis revealed the involvement of bilateral dorsolateral cerebellar regions during the entire 6 second time course of pitch memory processing. This tasked appears to be sensitive enough to detect functional differences in auditory processing following a one week training (Study B and D) and reveal differences between males and females (Study E) and musicians and non-musicians (C). Furthermore, using a pure behavioral experimental design, sleep seems to influence the performance on this task (Study F).

General aim 2: *Modification of the sparse temporal sampling method in order to assess the time course of cerebral activity (for the developed task)*

A sparse temporal sampling technique originally developed by Hall et al. (1999) was redefined and modified. By employing this method, the functional anatomy and the time course of cerebral activations of the pitch memory task were obtained without any interference with the scanner noise, enabling disclosure of the activation pattern of the given pitch memory task over a 6-second interval. As a result, the complete functional network was revealed, and different processing stages at different imaging time points could be pinpointed. The here presented studies could characterize differences of auditory processing for the different imaging time points in relation to performance, gender and musicianship (Study A and Study C-E). Further studies can employ this method in order to assess processing differences between and within groups in greater detail.

General aim 3: *Assessment of training- induced functional brain changes in the auditory domain (for the developed task)*

This body of research suggests that auditory learning triggers the use of a more efficient network by increasing activity in regions that are integral for pitch discrimination and pitch memory and decreasing activity in brain regions associated with attention and working memory (study B). Moreover, there is a strong relationship between the observed functional plasticity and the obtained performance score following the one week training period (see also aim4). The findings of study B corroborate the "scaffolding and storage" framework proposed by Petersen et al. (1998), which will be further described in chapter 15 and linked to the data presented here.

General aim 4: *Assessment of the influence of performance on functional brain patterns for the auditory domain. (for the developed task)*

By regressing the performance score in the pitch memory task with task-related MR signal changes, the supramarginal gyrus (with a greater inclination toward the left side than the right side) and the dorsolateral cerebellum were significantly correlated with good task performance (Study A). Furthermore, functional changes following a one week auditory training period were strongly correlated with the behavioral improvement in the auditory task (Study B). Following the one week training period,

increased activation of the left supramarginal gyrus was found only in those subjects who showed profound improvement in the assigned pitch memory task ("strong" learner). Activation increases in memory related regions, e.g. hippocampal regions were found in "weak" learner, who did not improve more than 5% in average. Despite performance matching, functional differences between males and females (study E), musicians and non-musicians (study C) and trained non-musicians and musicians were found. Since functional changes due to differences in performance can be ruled out in these groups, the results strongly suggest a difference in auditory processing between these groups. These findings underscore the necessity of correlating behavioral improvement with brain signal changes in order to determine differences in auditory processing and learning associated changes. Further studies must determine whether the influence of behavioral correlates on functional activity is as strong for other domains as it is for the auditory domain.

General aim 5: *Assessment of the role of musicianship in auditory processing (for the developed task)*

In addition to functional differences, previous studies assessing musicians and non-musicians revealed behavioral differences between the two groups. Thus, the observed functional differences might be due to either differences in functional or structural anatomy or actually behavioral scores. As study C indicates, a comparison of musicians and non-musicians reveals that musicians activate a network that includes auditory short-term memory regions (e.g. SMG) and regions implicated in visual-spatial processing (e.g. superior parietal cortex). When the reverse contrast is applied non-musicians appear to rely more on a network that includes brain regions important for pitch discrimination (e.g. Heschl's gyrus) and traditional memory regions (e.g. hippocampal gyrus). Given that both groups were matched in performance and did not show any significant brain asymmetries, these results indicate perceptual and/or cognitive processing differences between musicians and non-musicians. Both processing strategies seem to lead to similar performance scores in this pitch memory task. Long-term musical training thus appears to influence the neural networks used for successful performance on this pitch memory task.

Furthermore, study D revealed persistent functional differences between musicians and non-musicians following a one week training period for the non-musician group. Interestingly, the between group differences changed in response to

the training, leading to stronger differences in left primary and secondary auditory areas after the training. Given that there were no more activity differences in the supramarginal gyrus as a result of the training of the non-musicians, the processing network appeared to be more efficient and "musician-like" following the training period. Nevertheless, as study C already revealed, the trained non-musicians still relied primarily on primary and secondary auditory areas in order to achieve the same performance level.

General aim 6: *Assessment of the role of gender in auditory processing (for the developed task)*

The processing of this pitch memory task revealed more left than right lateralized processing during the early "receptive" phase in males compared to females. According to several reports, activations occurred in regions with gender related structural brain differences, such as the superior temporal gyrus, the frontal operculum, and the cerebellum. Females showed more activation than males in the posterior cingulate/retrosplenial region, possibly indicating a gender difference in the memory component of the here used task. Since neither group differed with regard to their performance, the possibility of using performance differences to explain the activation differences is eliminated. However, the gender differences observed in study E might also indicate a difference in perception or strategy in solving the pitch memory task.

General aim 7: *Assessment of the role of sleep in auditory processing (for the developed task)*

Confirming the findings of previous studies in the visual and motor domain, study F could demonstrate that sleep enhances delayed learning of an auditory pitch memory task following the initial training period. Regardless of whether subjects were trained in the morning or evening, delayed improvements occurred only across a night of sleep and not across a time of wakefulness. This study's findings therefore suggest that sleep plays a critical role in the consolidation of an auditory skill task. This adds important information to the growing body of literature that has shown the influence of sleep on learning mainly for procedural tasks. However, these findings also underscore the necessity to consider the influence of sleep on learning in future studies assessing training related functional plasticity.

Overall, the general aims proposed in chapter 4 were partly achieved. Nevertheless, further research must continue to investigate auditory processing in general, experience-induced functional plasticity as well as the influence of musicianship, gender and sleep. The following chapter will discuss the specific role of the supramarginal gyrus and the cerebellum in auditory processing.

14. The role of the supramarginal gyrus and the cerebellum in auditory processing

As already discussed in chapter 13, the supramarginal gyrus and the cerebellum appear to play an important role in successfully performing the pitch memory task. When the parameter estimates were weighted with the mean corrected performance data of each subject in Study A, activity in the SMG emerged as positively correlated with higher accuracy in the pitch memory task for the first two time point cluster. This effect was much stronger in the left than in the right brain hemisphere. Within the last ITP cluster, activation in the left cerebellum, including the posterior part of lobule VI, also was positively correlated with the performance score. Furthermore, training-induced functional changes in study B were strongly related to the improvement scores in the pitch memory task. Increased activation of the left supramarginal gyrus following the training was found for "strong" learners in compared to "weak" learners. The next two sections will discuss the role of the supramarginal gyrus and the cerebellum in auditory processing.

14.1 The SMG- a general auditory memory and selective attention module?

The supramarginal gyrus (SMG) is located around the superior termination of the lateral sulcus in the parietal lobe. Collectively with the angular gyrus, these two gyri are called the inferior parietal lobe. Early lesion studies involving the left or right hemisphere revealed a variety of neuropsychological dysfunctions, including conduction aphasia (Geschwind et al., 1965; Brown et al., 1972), acalculia (Lezak et al., 1976), or Gerstmann's syndrom (Critchley, 1966; Fogel, 1962; Curtis, 1962). Research conducted within the last ten years provided more evidence demonstrating the importance of the left SMG for short-term auditory-verbal memory processes, phonological storage and other language related tasks (e.g., Jobard, et al., 2003; Roux et al., 2003; Duffau et al., 2003; Hashimoto & Sakai, 2003; Pillai et al., 2003; Kim et al., 2002; Simon et al., 2002; Thierry et al., 1999; Salmon et al., 1996; Vallar et al., 1997; Caplan et al., 1995; Paulesu et al., 1993; Clarke et al., 2000). In addition to processing of verbal stimuli some studies found involvement of the SMG in auditory oddball tasks (e.g. Yoshida et al., 1999), auditory discrimination (Kikuchi et al., 1997)

and auditory memory tasks (Celsis et al., 1999; Sakurai et al., 1998; Breier et al., 1999).

Based on studies A and B, which revealed activation of the SMG in relation to good task performance, one can conclude that this structure might be more a module for general auditory memory than for specific verbal memory processing. In study A, superior performing subjects relied more on this general auditory memory module, and the recruited network ensured better task performance during the scan. The performed study B also provides evidence for this theory, because successful learning of a pitch memory task led to increased activation of the SMG in the post-training scans. Furthermore, subjects with minor improvement scores following the training period showed no recruitment of the SMG after the training period. For the developed pitch memory task, the SMG appears to be the most important and efficient network component. A study by Callan et al. (2003) could also reveal increased activation of the supramarginal gyrus following training of a difficult second-language phonetic contrast. Increased activation of the SMG in professional musicians (Study C) provides further evidence, suggesting the use of a more efficient network as a result of long-term training of auditory processing in this group. Further studies assessing verbal and non-verbal short-term memory together, might reveal a conjunction between verbal and general auditory memory or memory for environmental sounds based in the inferior parietal lobule.

Nevertheless, based on the literature regarding selective attention, one can infer an additional explanation for the increased use of the SMG in good performers, “strong” learners and professional musicians.

According to Linden et al. (1999), this structure also appeared to be involved in target detection. Typically, the neural response patterns that are required for an appropriate behavioral reaction to subjectively relevant changes in the environment are studied by oddball paradigms, which require the subject to detect infrequent target stimuli within a train of frequent standard (non-target) stimuli. As Linden and colleagues revealed, activation of the SMG occurred only in relation to the target and not the standard stimuli. Downar et al. (2001), found the SMG to be involved in identifying features of auditory sensory input, which showed a potential relevance to behavior. Further evidence for the SMG being involved in target attention of auditory stimuli revealed Sevostianov et al. (2002). Using an oddball task as well, the authors revealed that the SMG was activated when selectively attending to target tones. Based

on this findings, one can also infer that the SMG is an integral structure for auditory selective attention. Increased activation of the SMG during the pitch memory task might improve one's ability to carefully monitor and listen to the six or seven tones and identify possible identical tones within one sequence. Nevertheless, the delayed visual prompt in this task requires auditory short-term memory in order to make the required decision. Thus, the here conducted studies are not able to identify the exact role o the SMG in pitch memory, but they suggest that the SMG may be involved in general auditory short-term memory processes as well as auditory selective attention.
In addition to the SMG, the cerebellum seems to be an important network component involved in pitch memory processing. The following section seeks to link the presented data with previous found evidence regarding the involvement of cerebellar regions in auditory processing.

14.2 The cerebellum- a structure for auditory sequential processing?

The cerebellum has been neglected for centuries. Located at the lower back of the brain, this fist-size structure is now being reevaluated in many ongoing studies. Originally, this structure was thought to have only motor functions, but a broader view of its functions has emerged during the past decade. The dominant dorsal cerebellar activation revealed in study A was somewhat surprising, although in agreement with studies indicating that the cerebellum has non-motor functions (Bower, 1997; Jueptner et al., 1997c; Parsons & Fox, 1997; Desmond et al., 1998; Penhune et al., 1998; Satoh et al., 2001; Schmahmann & Sherman, 1998) Particularly intriguing is the involvement of the cerebellum in auditory tasks such as the planning of speech production (Silveri et al., 1998), auditory verbal memory function (Grasby et al., 1993), tone recognition tasks (Holcomb et al., 1998), and multiple musical tasks, including musical tempo, duration discrimination (Parsons, 2001; Hughdahl et al., 1999; Perry et al., 1999; Riecker et al., 2000) and imagined musical rehearsal (Langheim et al., 2002). Satoh et al. (2001, 2003), revealed bilateral activation of the cerebellum in a harmony listening task but not in a soprano or alto-part-listening task in non-musicians. By contrasting singing versus speaking, Jeffries et al. (2003) revealed cerebellar activation, indicating a different network, which included involvement of the cerebellum in the more musical task. Furthermore, some studies reveal activation of the cerebellum in auditory short-term memory functions. Zhang et

al. (2003), for instance, showed activation of the dorsolateral cerebellum in retrieval of middle but not recent items in an item list. Additionally, the cerebellum appears to play a role in the perception of timing and duration of auditory stimuli, auditory rhythm reproduction and auditory pacing stimuli (Pastor et al., 2002; Mathiak et al., 2002; Jancke et al., 2000a; Johnsrude et al., 1997; Penhune et al., 1998). In lesion studies, patients with a degenerated cerebellum struggled with pitch discrimination tasks (Parsons, 2001) and Riva et al. (2000) found that children with right cerebellar tumors presented disturbances of auditory sequential memory. Based on this literature background, one can clearly conclude that the cerebellum plays a role in general auditory processing and auditory timing, in particular.

The results of presented body of research (Study A-E) provide additional evidence for this and thus may aid in further assessing the role of the cerebellum in auditory processing in more detail. In study A, the time course of pitch memory revealed activation of the cerebellum for all three time point clusters. By contrasting the last ITPs to the initial time points, bilateral activation of the dorsolateral cerebellum was seen, corroborating the strong activation of the cerebellum throughout the entire time course. A regional analysis showed positive activation of the cerebellum for all seven imaging time points. Activation of the bilateral dorsolateral parts of the cerebellum were correlated with good performance in the pitch memory task. Each of the other assessed regions achieved a clear peak of activation and an accompanying decrease following that peak. Based on the aforementioned literature regarding the role of the cerebellum in auditory processing, one can surmise that the cerebellum might be involved in the ongoing activity of pitch discrimination while subjects perform the pitch memory task. This may explain the cerebellar activation in both the initial time points and throughout the task. In order to attain a high performance level in this task and perform the required pitch discrimination, subjects must monitor the entire pitch sequence. When Griffiths et al. (2001) asked subjects to make a same/different judgment while comparing pitch sequences of 6 tones, they found a more extensive right lateralized network including cerebellum, posterior temporal and inferior frontal regions. Furthermore, subjects reported a sequential comparison between the first target one and each subsequent tone when asked about their strategy in study A. The role that the cerebellum plays in timing and pacing of auditory stimuli, according to the literature, supports this theory of involvement of the

cerebellum in the ongoing sequential auditory analysis and possible discrimination of the six or seven tones.

Furthermore, by lowering the threshold in the contrast post-training versus pre-training in "strong" learner versus "weak" learner in study B, activation of the cerebellum becomes significant. Subjects who improved by an average of 15% following the training period relied more on the cerebellum in the post-training scan in comparison to the pre-training scan. Callan et al. (2003) could also demonstrate an increased activation of cerebellar regions following training of a difficult second-language phonetic contrast.

Although musicians activated the cerebellum bilaterally when performing the task in study C, non-musicians showed greater right hemispheric cerebellar activation than professional musicians. One possible explanation for this is that the network for auditory processing in musicians is more efficient due to long-term auditory training, which might trigger experience-induced decreases in activation of cerebellar structures in a direct comparison between the two groups (see also chapter 15). Nevertheless, when trained non-musicians are compared to musicians (study D), activation of the cerebellum no longer differs. Hutchinson et al. (2003) revealed significantly greater absolute and relative cerebellar volume in male musicians in comparison to matched non-musicians, this did not prove to be the case for total brain volume. Furthermore, lifelong intensity of musical practice correlated significantly with relative cerebellar volume. This effect could not be observed in the female group. Though a modulation of these effects seems to occur according to the subject's gender, the authors infer that particular regions of the cerebellum play important roles in music processing and may be altered over time as a result of music training.

This is consistent with the results of study D, where males had more cerebellar activations with regard to this pitch memory task than female subjects did. Nonetheless, the role of gender in musical processing in the cerebellum has remained unexplored. Given that male subjects exhibited a greater right cerebellar activation, (which is possibly related to a greater left lateralized activation in the perisylvian region not seen in females), males appear to employ a more lateralized processing strategy.

Overall, these results suggest that specific cerebellar regions play an important role in auditory processing, including pitch discrimination, musical processing and sequential ordering of auditory information Furthermore, cerebellar structures seem to

show a structurall and functional adaption to training, and gender seem to modulated some of the observed structural and functional effects.

15. A model for performance related functional plasticity in the brain

As described in this paper's introduction, numerous experiments conducted over the last thirty years have indicated that cortical representations are continually shaped by experience (e.g. Weinberger, 1993; Merzenich et al., 1996; Buonomano & Merzenich, 1998; Edeline, 1999). The number of cortical neurons that respond to task-relevant stimuli actually increases as a result of behavioral training for discrimination tasks that engage a limited sensory region (e.g. Jenkins et al., 1990; Recanzone et al., 1992; Recanzone et al., 1993). The demonstrated correlations between cortical map organization and experience-induced behavioral improvements in animals suggest that cortical plasticity contributes significantly to, at a minimum, perceptual learning. Additionally to the results of animal research, human research elucidates continuous optimization of cortical networks in response to changing of behavioral needs. Overall, cortical plasticity appears to be involved in improvement of behavioral skills, maintenance of specific sensory representation, in recovery from brain damages as well as in the compensation for early and late sensory loss. While Hebb's rule (see section 2.1) can explain some of the experimental findings, it cannot account for reorganization of entire cortical networks in response to experience, damage or sensory loss. In order to explain how learning occurs in large populations of neurons and in cortical networks, which consist of millions of neurons and connections, theoretical and empirical research must be conducted in the future.

This section aims to incorporate studies A to F into a theoretical framework proposed by Petersen, et al. (1998), which seeks to explain the effects of practice on the given task's functional anatomy.

15.1 The "scaffolding and storage" framework

In general, the results of the studies A-F support a framework proposed by Petersen et al. (1998), which is based on the assumption that unskilled and skilled performance of a particular task represents the performance of " different tasks" in a neurobiological sense and thus triggers the involvement of different brain regions.

The authors propose the "scaffolding-storage" framework based on theoretical and empirical implication from the literature as well as their results of training studies using verbal and motor tasks. The authors describe two different but not necessary

exclusive, general concepts related to skill acquisition. The first concept is based on the assumption that learning occurs through and as a consequence of the use of more specific "neuronal circuits". With regard to synaptic plasticity, this is roughly equivalent to the Hebbian rules, which describes that modifications in the synaptic transmission efficacy are driven by correlations in the firing activity of pre-and postsynaptic neurons (specific neuronal circuits). According to the findings of several other studies, learning might occur in different stages, and the particular skill to be learned might be programmed at varying levels of complexity (Fitts, 1964; Posner & Keels, 1968; van Mier et al., 1993a,b). This can be illustrated by the example of learning to ride a bike. Comparisons of beginner level riding and advanced level bike riding typify qualitatively different tasks. Furthermore, the different stages of this learning process might involve different brain regions and/or alter the degree to which certain neural substrates are involved. As Petersen et al. (1998) argue, these two concepts - circuit-efficiency and processing differences - are not exclusive, and both mechanisms play an important role in skill acquisition.

On the basis of their research as well as those of others, the authors hypothesize that a "scaffolding" set of brain regions might be employed for unskilled, yet strenuous, performance in order to cope with the new task demands. Because task-related processes and mechanisms might be stored more efficiently following practice, necessary sets of programs might be assessed in a different way (storage stage), resulting in a change of the neural network or the degree of activation with improved performance.

Furthermore, Petersen et al. (1998) introduced two possible mechanisms for explaining the transfer from the "scaffolding" to the "storage" stage. According to the first mechanism, both, "scaffolding" and "storage" areas are active in parallel throughout all stages of learning, and that practice modulates the balance of activity within and between pathways (parallel mechanism). As the principle of the second mechanisms suggests, the essential or exclusive activation of one particular set of brain regions during the early stages of learning results in a shift to a different set of brain areas, which represents a more efficient network within the later or overlearned stages of learning (exclusive mechanism).

By integrating their research result into the proposed framework, the authors seek to test their theoretical assumptions empirically. First, they state that activity occurring within the brain areas activated during early stages of learning ("scaffolding

areas") is present throughout the entire time course of learning. This observation appears to be consistent with the first mechanism (parallel mechanism). However, because none of the subjects showed a ceiling effect, it appears that none of the tasks were overlearned. Nevertheless, one of their overlearned control tasks (reading) appears to inhibit areas that were recruited during a "scaffolding" stage of a verb generation task. Therefore, it seems unclear which of the two, or if even both mechanisms are involved in successful skill learning. Consequently, further studies must address this issue. Furthermore, more research studies are needed in order to identify specific brain regions within the "storage set" for certain tasks.

15.2 The scaffolding and storage" framework: contributions from the auditory domain

In addition to the studies conducted by Petersen et al. (1998), numerous studies from the motor domain reveal evidence for the proposed framework. First, this framework is supported by a set of single-unit recording studies in animals showing that certain cells increase their firing in an initial, early learning state (Mitz et al., 1991; Ojakangas & Ebner, 1992; Chen & Wise, 1995), while other cells show a decrease in firing as a result of additional training (Ojakangas & Ebner, 1992; Llungberg et al., 1992; Chen & Wise, 1995). Second, human studies provide some evidence for "scaffolding" and "storage" areas as well as increases and decreases in relation to motor skill training (Jenkins et al., 1994; Schlaug et al., 1994; Jueptner et al., 1997a,b, c; Toni et al., 1998; Karni et al., 1995, 1998; van Mier et al., 1998; Doyon et al., 1996; Hazeltine et al., 1997; Grafton et al., 1995). The following section seeks to integrate the existing results from the auditory learning domain in humans as well as Study A-F of this body of this project into the "scaffolding and "storage" framework.
As for the motor domain, there seems to be a strong relation between the performance improvement or stage of learning and the neural activity in certain brain regions within the auditory domain. Most of the studies revealed an activity increase in the initial training phase referring to the "scaffolding" phase and a decrease of activity as learning progressed and the task becomes more 'automatic' or 'overlearned'.

Cansino & Williamson (1997) only trained one single subject in a frequency and intensity discrimination task and showed activity decreases in primary and association auditory cortices after a long-term training in comparison to a naïve state

before the training. The behavioral results indicate that the more than 200 hours of training over a time period of more than 60 days led to a somewhat 'overlearned' state. The revealed activity decrease in this study can be explained with a transfer from the "scaffolding" to the "storage" stage in Petersen's framework, induced through the intensive learning that consisted of over 75.000 trials. Furthermore, this results support the idea of a parallel mechanism for the transfer from "scaffolding" to "storage" areas, where both, "scaffolding" as well as "storage" areas are active in parallel throughout all stages of learning and practice seems to modulate the activity relation within and between pathways. Nevertheless, this study only investigated auditory evoked neuromagnetic fields within the primary and association auditory cortices, which makes it impossible to assess a possible change of brain regions involved in this auditory task (exclusive mechanism).

In addition to the training results, the authors looked within three subjects at activity differences in relation to different difficulty levels as well as correct versus incorrect answers. Interestingly, when discrimination was not better than 50% correct answers, evoked field patterns manifested no significant differences between correct and incorrect responses. However, when the performance score reached a level of at least 75% correct answers, incorrect responses led to stronger neuromagnetic evoked responses.

These results are also in accordance with the Petersen et al. (1998) framework indicating a possibly faster, more effortless and automatic processing for the easier trials, representing a "storage" stage, which is associated with a weaker amplitude.
In an oddball study, Menning et al. (2000) could reveal an increase in strength of the cortical source and amplitudes over the time course of a frequency discrimination training for deviants of 5 Hz, 10 Hz and 50Hz in comparison to a 1000 Hz standard tone. For the deviant 50 Hz, the neural correlates decreased at the end of the training. The authors did also not obtain behavioral results in the MEG sessions, so that it remains unclear whether any of this frequency differences were 'overlearned'. One possible explanation could be, that following the training the response to the smaller deviants are still in a "scaffolding" stage whereas the response to the 50 Hz deviant already reached the "storage" stage. However, three week after the training all subjects showed a decrease in activation for all three deviants, which is somewhat controversial to the model.

Using a similar oddball task, Jancke et al. (2001) showed a decrease of the hemodynamic responses in the auditory cortex and association areas following a one week training only for those subjects, which improved during the training ("good performers"). Furthermore, this activation changes were strongest for those stimuli accompanied by the strongest performance gain.

With respect to the hemodynamic responses in the auditory cortex, there was no difference for those subjects whom did not exhibit improved performance ("bad performers") and the control group, which did not receive pitch discrimination training. The results among the "good performers" indicate a switch from "scaffolding" to "storage" stages. Hemodynamic changes were only obtained for auditory areas including the planum temporale, planum polare and the superior temporal sulcus, and therefore a possible change in network components was not assessed. Furthermore, the results for the additional two groups revealed a "scaffolding" stage in both the pre-training and the post-training scans. Thus, while training *per se* does not appear to induce the switch between the two stages, the performance level seems to trigger the change from " scaffolding " to "storage" areas or change the balance between the two.

Overall these studies indicate that increased activity within primary auditory and auditory association areas is triggered by performance score, rather than training *per se*. This is accompanied by decreased activity after reaching a superior performance level or automatic state, which might be explained by a change in either network components or the degree of activation within the same network components. In order to further explore these issues, the following section seeks to integrate Studies A-F into the framework.

In study B of this body of research, subjects underwent training for a pitch memory task during a one week period. According to preliminary analyses, there was a high variability of the trained subjects' improvement scores. Based on their improvement scores, the subjects were divided into "strong" learner and "weak" learner groups Given the decrease in parietal areas and the increase in left hemispheric auditory areas following the training, one can surmise that all subjects in the "strong" learner group changed from a scaffolding set of regions to a more efficient "storage" set of regions with regard to the "scaffolding and storage" model. Nevertheless, increased activity in the auditory areas suggests that within this group of "strong" learner that the full "storage" state might not be reached yet. This is

supported by an intermediate level of performance and the absence of a ceiling effect following the training period. Decreased activity in parietal regions within this group suggest a change of network components following the training period.

Contrary to what the study of Jancke et al. (2001), disclosed, the study revealed training-induced signal changes even in those subjects who only improved by an average of 4%. In terms of the "scaffolding" and "storage" framework, the strong increase in various areas (particularly memory-related areas) and the performance score indicate that subjects in the "weak" learner group still used a "scaffolding" set of regions following the training period. But because this group, unlike the "strong" learner group, activated new areas following the training period, one can conclude that learning resulted in this group in a different set of "scaffolding" areas. This change of network components does not appear to be efficient for successfully performing the task.

This now raises the question as to why the "scaffolding" set switched to those particular, more memory related areas. Further studies must address this question.
Interestingly, when comparing the post-training with the pre-training scans, only the "weak" learner and the control group exhibited an increase in working memory regions within the frontal lobe, although the regions involved differ slightly. Overall, this strategy does not seem to be successful, since behavior did not change significantly for both groups.

This strongly supports the hypothesis that the "strong" learner switched from a "scaffolding" stage to a "storage" stage, which involves only regions integral to successful performance o the assigned task. Given the profound changes in the "weak" learner group, the training period induced a strong, positive change. These effects are not the result of simply scanning one subject twice (repetition effect). When the improvement effects in the "strong" learner were compared to the "weak" learner, the SMG (as well as the cerebellum when lowering the threshold) became highly significant, identifying these structures as the key regions within the "storage" network for successful performance.

In study A, the SMG and the dorsolateral part of the cerebellum were highly positive correlated with the performance score. One could argue, that the good performers in study A were equipped with a "natural" set of "storage" skills and an efficient network, which could also be induced by a one week training for that particular task (Study B).

Study C assessed whether musicians in comparison to non-musicians were equipped with a different set of "storage" skills as a result of their extensive training. According to previous studies, these two groups show differences in auditory processing. These findings were interpreted with a more efficient network as a result of the intensive training in musicians, but those studies did not control for performance differences between the groups. In Study C, a group of musicians was matched with a group of good performing non-musicians in terms of performance scores in the pitch memory task. Compared to the non-musicians, the musician group showed greater activation of the SMG. But the reverse contrast revealed increased activation of primary auditory areas for the non-musicians. These results indicate auditory processing differences even in two groups that were matched in terms of performance scores. The "natural" set of storage skills in musicians seems to differ from the set of "storage" skills within the non-musicians, which could be a result of the lifelong training in the musician group.

However, this is inconsistent with the assumption that the performance score, rather than training *per se*, triggers increased activity within primary auditory and auditory association areas, which is accompanied by decreased activity after a superior performance level or automatic state is reached. The question now is whether an intensive training period for non-musicians can facilitate a "storage" network similar to that of musicians or whether musicians have a predisposition-related difference in the network. Study D addressed this issue.

In study D, the "strong" learner from study B were compared to musicians, prior and following the one week training period. Following the training period, however, musicians and non-musicians no longer exhibited any differences in the SMG. This suggests, that both groups are now activating the key region SMG. Furthermore, non-musicians activated more left hemispheric primary and auditory areas than the musicians did. Previous studies revealed that a change in activation from the right to the left hemisphere occurred as a result of increased musical sophistication. From this, one can surmise, that the training triggers this switch from the right to the left hemisphere or, in other words, from a "scaffolding" to a "storage" set of regions. The increase in activation in the left auditory cortex in the trained non-musicians in comparison to the musicians would corroborate the notion that a superior performance level or automatic state triggers activity decreases within auditory areas,

but both groups were matched for performance scores. Therefore one can argue that musicians "naturally" might have a more efficient network for this pitch memory task The revealed gender differences in Study E and language differences found when comparing males and female in various studies, suggest gender differences in the "scaffolding" set of regions, and further studies have to assess whether those differences persist following a training period.

Furthermore, the influence of sleep on learning has been demonstrated by Study F as well as other studies. To date, no study has assessed the specific influence of sleep on the neuronal correlates of auditory learning. Subsequent studies should address this issue, particularly the role played by sleep within the "scaffolding and storage" framework. Sleeps might prove to accelerate the switch between the two stages.

Overall, most of the studies assessing the neural correlates of learning can be integrated into the proposed framework. Learning seems to alter the functional network of a particular task, which could be accompanied by activity increases in specific areas during the beginner and intermediate levels of learning and decreased activity once a superior level or automatic state is attained. Nevertheless, some regions (e.g. parietal regions) appear to indicate a decrease relatively early within the course of learning. In addition, learning effects can be observed in the absence of a behavioral improvement and further studies should include behavioral correlates in the analysis in order to detect performance related differences of neural correlates. Furthermore, there appear to be differences in the "scaffolding" and "storage set of regions in relation to gender and musicianship.

In order to specify the neuronal correlates of learning in more detail, future studies need to be conducted. A more detailed understanding of how sensory experience results in different forms of cortical reorganization will have important theoretical implications for contemporary theories of neural information processing and learning.

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17. Tables

Table 1: Results of the pilot study

Subject ID	*Session*	*Correct responses all trials (in %)*	*correct responses 5 distractors*	*correct responses 4 distractors*
TZ	1	63.75	23	28
	2	68.75	28	27
	3	68.75	26	29
	4	72.5	30	28
AH	1	85	33	35
	2	96.25	40	37
	3	100	40	40
	4	100	40	40
AP	1	70	28	24
	2	65	24	22
	3	77.5	30	25
	4	82.5	32	28
RX	1	48.75	21	15
	2	53.75	23	16
	3	57.5	27	22
	4	52.2	28	28
AE	1	57.5	26	27
	2	62.5	25	28
	3	60	26	24
	4	66.25	28	28
MEAN	1	65	26.2	25.6
	2	69.25	28	26.8
	3	72.75	29.8	27.2
	4	74.69	31.6	30.6

Table2: Regional group mean t-values for all imaging time points (ITP) for selected regions of interest (HG = Heschl's gyrus; PT = planum temporale; SMG = supramarginal gyrus; Cer = cerebellum, lobule V and VI).

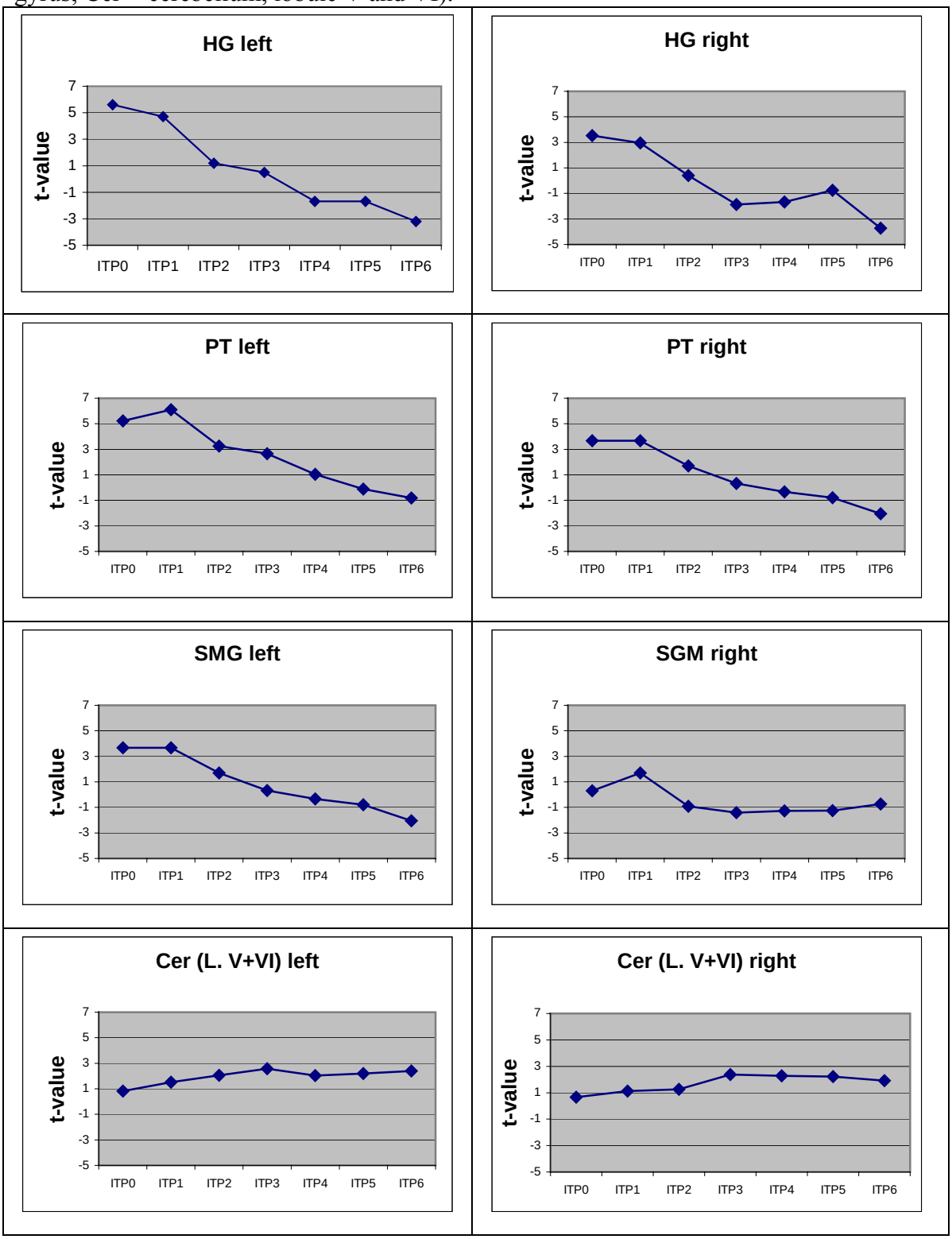

Table 3: Regional group mean t-values for all imaging time points (ITP) for selected regions of interest (HG = Heschl's gyrus; PT = planum temporale; SMG = supramarginal gyrus; Cer = cerebellum; IFG = inferior frontal gyrus; Post Cing = posterior cingulate/retrosplenial gyrus. Low or negative t-values in some regions might be explained by using average t-scores of the entire anatomically defined region. Nevertheless, gender differences (female= pink; male = blue) are evident in most of these selected regions.

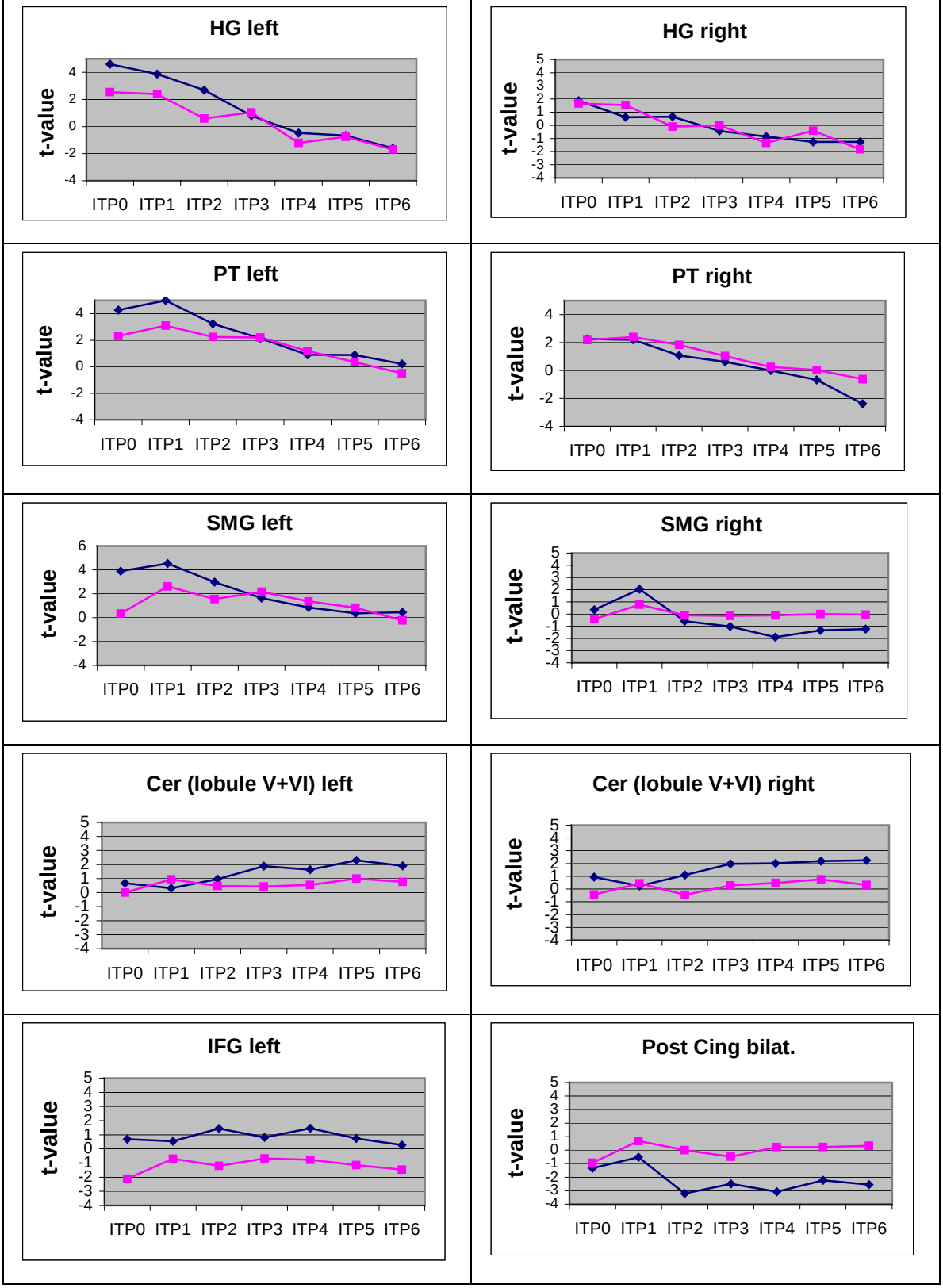

Table 4: Changes in Cluster centers after one and two iterations

Iteration	**Cluster**	
	1	2
1	6.786	3.714
2	0.00	0.00

Table 5: Cluster Center for the two Clusters

	Cluster	
	1	2
Improvement score (pre training –post training)	4.79	15.29

Table 6: Cluster solution for individual Subject

Subject ID	***Cluster***	***Cluster distance***
1	1	3.214
2	2	2.286
3	2	3.714
4	1	6.786
5	2	2.286
6	1	0.286
7	2	2.286
8	1	2.214
9	2	3.286
10	1	1.386
11	1	1.214
12	1	1.814
13	2	3.714
14	2	2.714

Table 7: Two-sample T-test results for the pre and post training session as well as the training sessions for "strong" learner "weak" learner. Learner show a significant better result in all tests except the initial pre training test.

Variable	*T-value*	*df*	*Significance (two-tailed) p=*
Pre training score	0.329	12	0.748
Post training score	4.131	12	0.001 *
Improvement score	5.980	12	0.000 *
Training Session 1	3.791	12	0.003 *
Training Session 2	2.376	12	0.035 *
Training Session 3	2.747	12	0.018 *
Training Session 4	2.660	12	0.021 *
Training Session 5	2.533	12	0.026 *

Table 8: ANOVA for the three groups for the pre training score

Variable	*F-value*	*df*	*Significance (two-tailed) p=*
Pre training score	0.391	2	0.681

Table 9: Two-sample t-test for the groups "strong" learner and "weak" learner for the dependent variable: Improvement scores

Variable	*t-value*	*df*	*Significance (two-tailed) p=*
Improvement score (pre training –post training)	5.980	12	0.000*

Table 10: Two-sample t-test for the groups " strong" learner and Control for the dependent variable: Improvement scores

Variable	*t-value*	*df*	*Significance (two-tailed) p=*
Improvement score (pre training –post training)	4.297	15	0.001 *

Table 11: Two-sample t-test for the groups "weak" learner and Control for the dependent variable: Improvement scores

Variable	*Tvalue*	*df*	*Significance (two-tailed) p=*
Improvement score (pre training –post training)	1.250	15	0.230

Table 12: Paired t-tests (pre training error rate and post training error rate) for the different frequency distances in the "strong" learner group.

Variable	*t-value*	*df*	*Significance (two-tailed) p=*
"same"	5.280	6	0.002*
diff1 (41.17 Hz)	2.554	6	0.043*
diff2 (44.64 Hz)	2.680	6	0.037*
diff3 (51.74 Hz)	1.382	6	0.216
diff4 (56.12 Hz)	0.947	6	0.380
diff5 (64.23 Hz)	3.240	6	0.180

18. Figures

Study A:

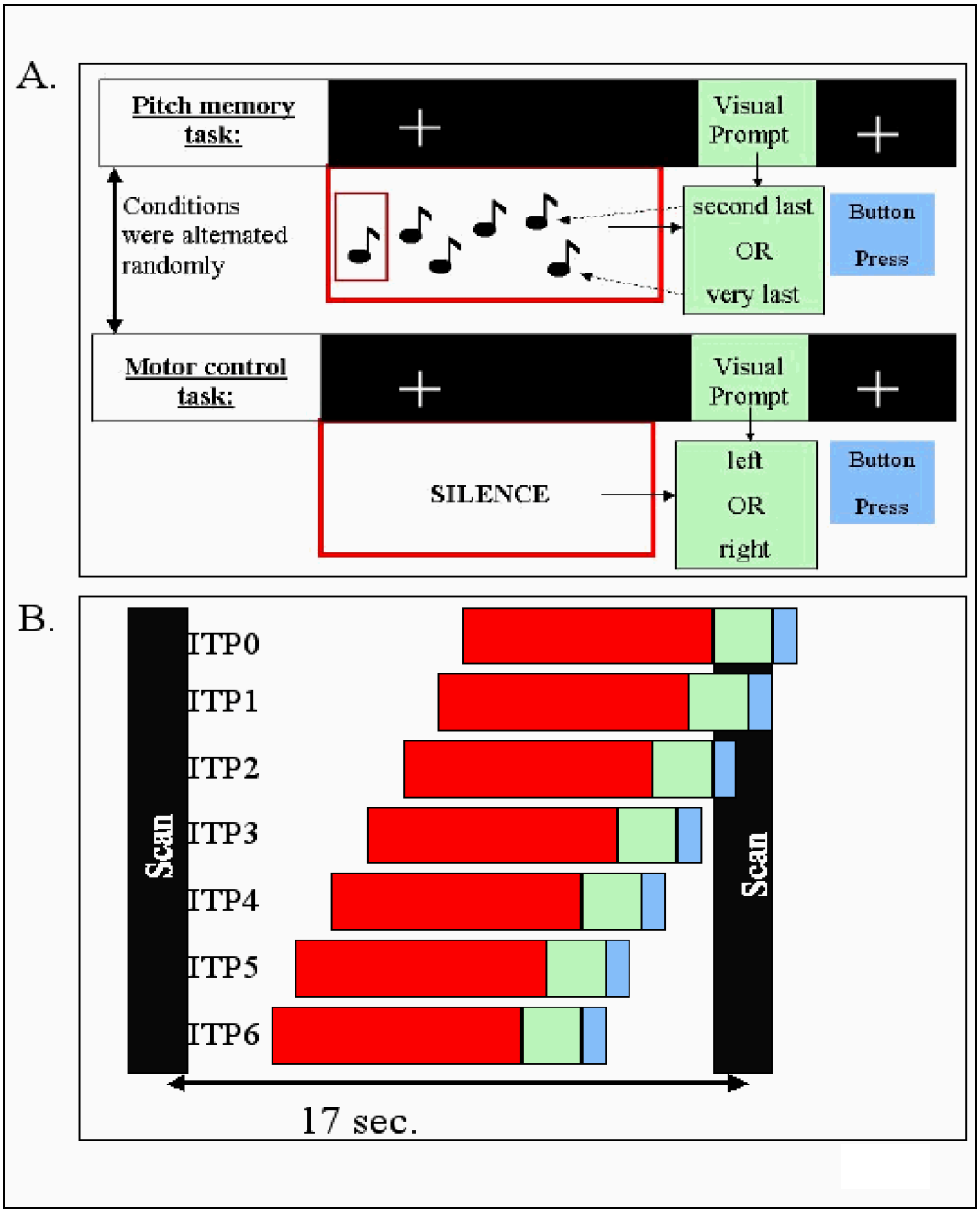

Figure 9: This schematic drawing demonstrates the task design (A) and MR image acquisition procedure (B) using a modification of a sparse temporal sampling technique (ITP = imaging time point).

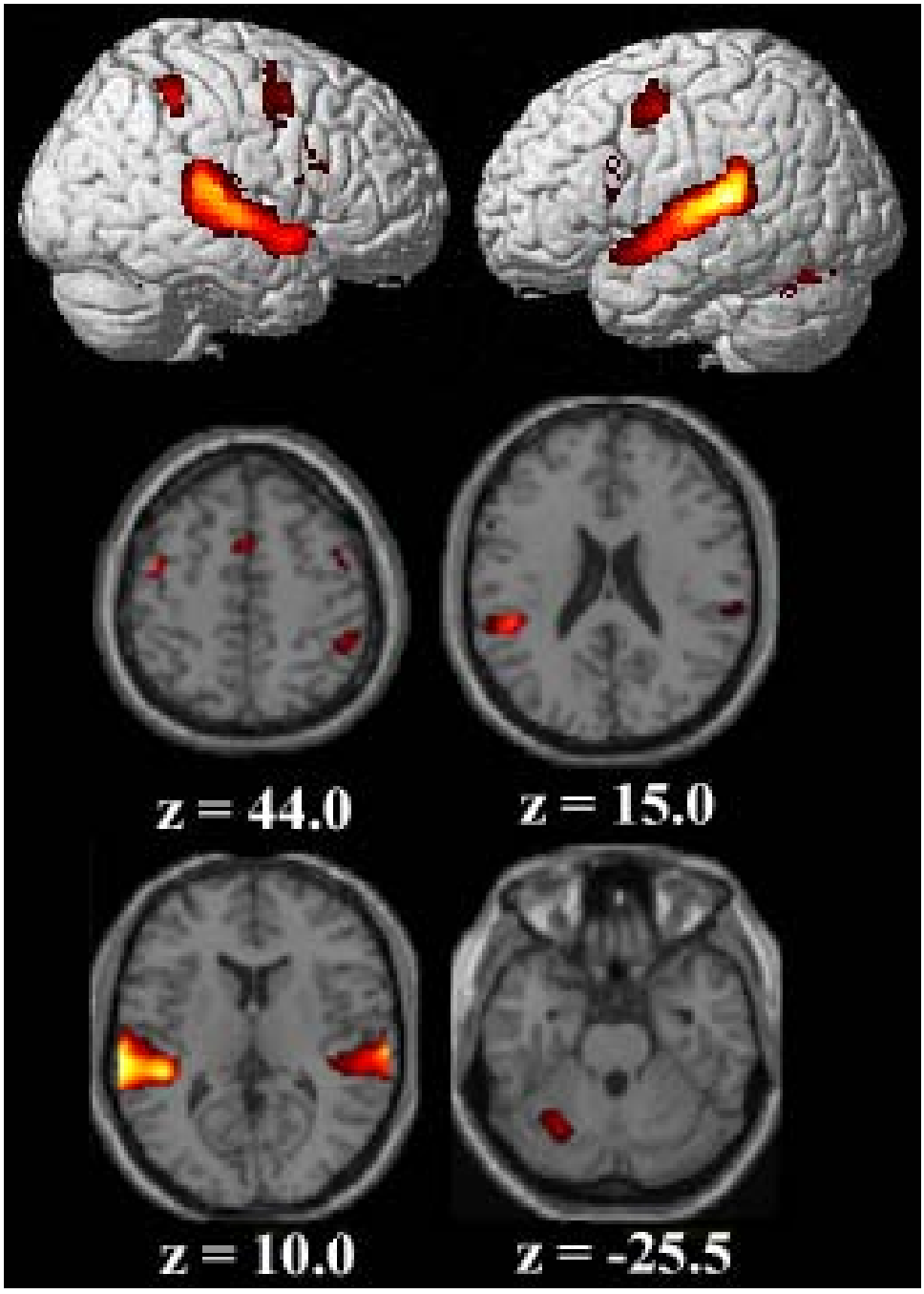

Figure 10: Brain activation pattern ($p < 0.05$, corrected) during the initial imaging time points 0-2 (0-2s after the end of the auditory stimulation).

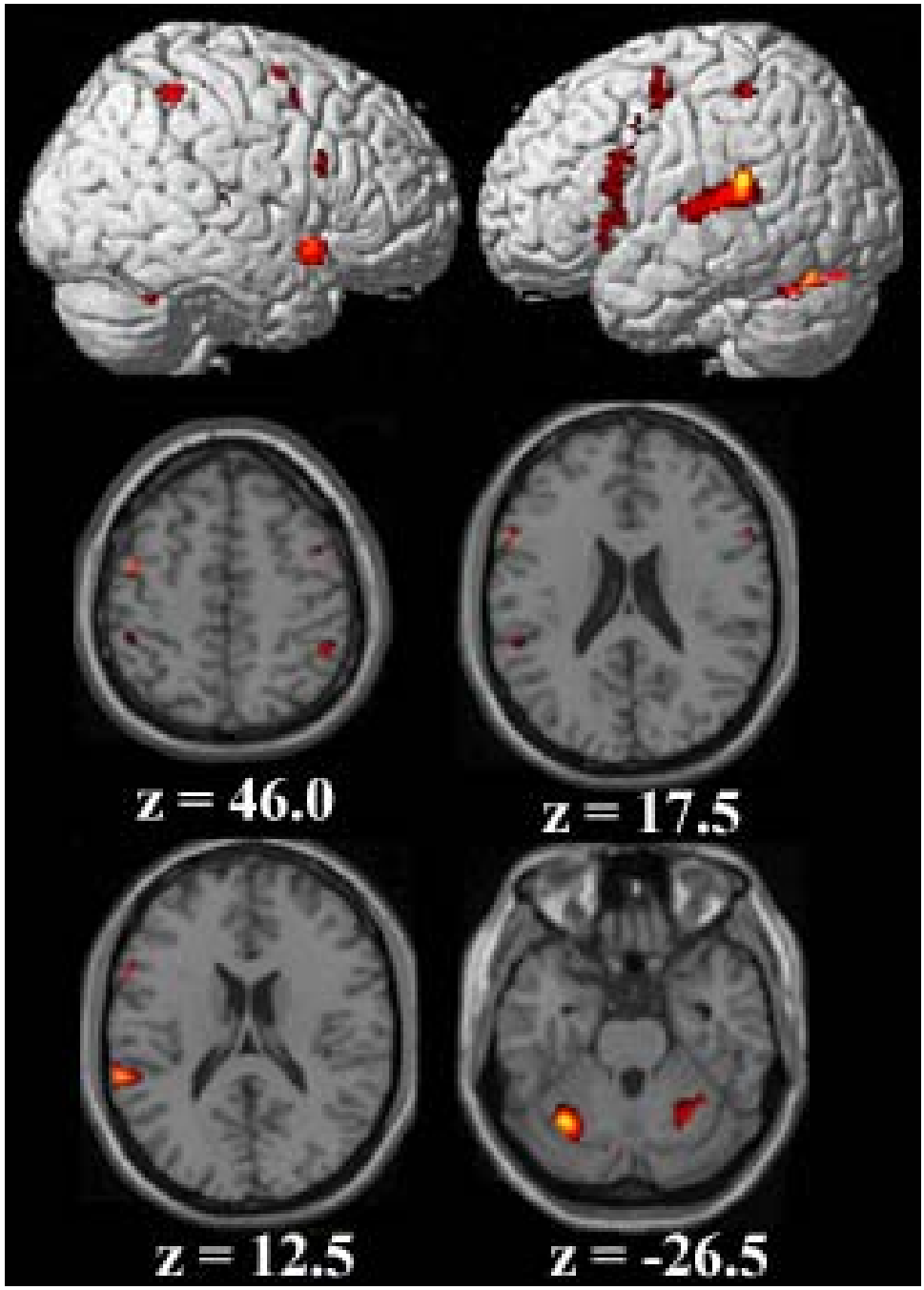

Figure 11: Brain activation pattern ($p < 0.05$, corrected) during the intermediate imaging time points 3-4 (3-4s after the end of the auditory stimulation).

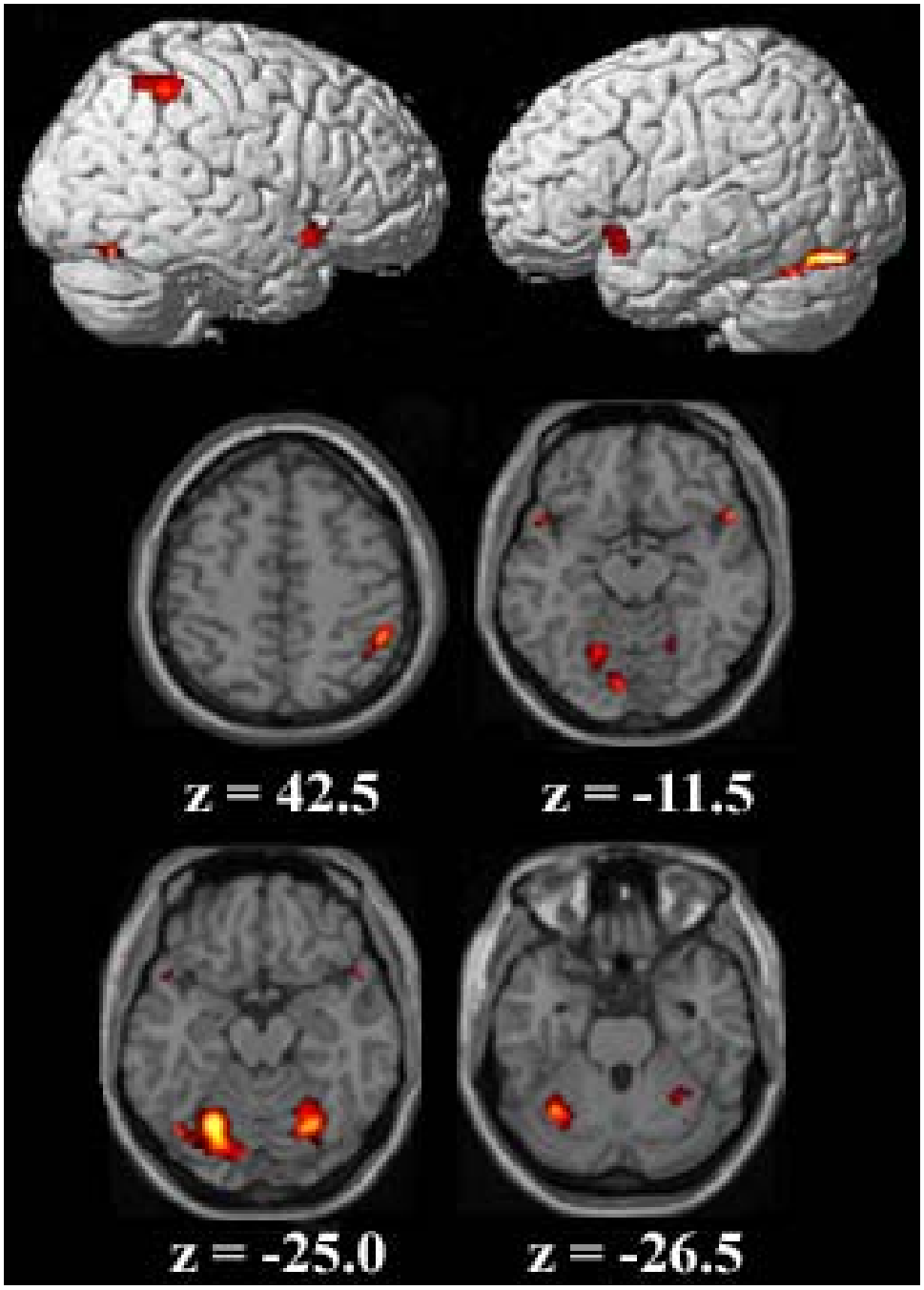

Figure 12: Brain activation pattern ($p < 0.05$, corrected) during the late imaging time points 5-6 (5-6s after the end of the auditory stimulation).

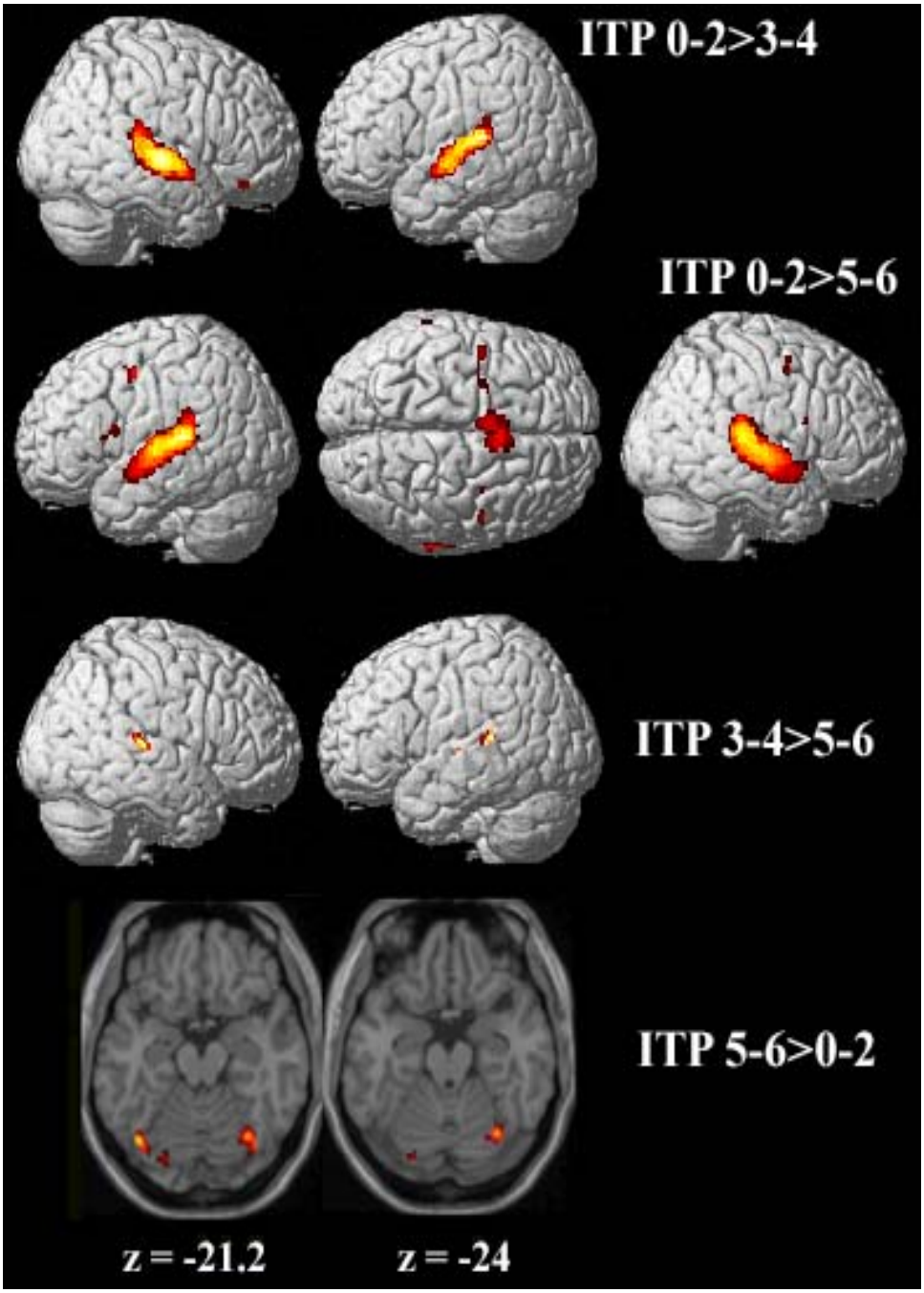

Figure 13: Brain activation pattern ($p < 0.05$, corrected) comparing initial imaging time points with intermediate (ITP 0-2>3-4) and late imaging time points (ITP 0-2>5-6). Brain activation pattern comparing intermediate imaging time points with late (ITP 3-4>5-6) and late imaging time points with initial imaging times points (ITP 5-6>0-2). All other comparisons did not show any significant activations.

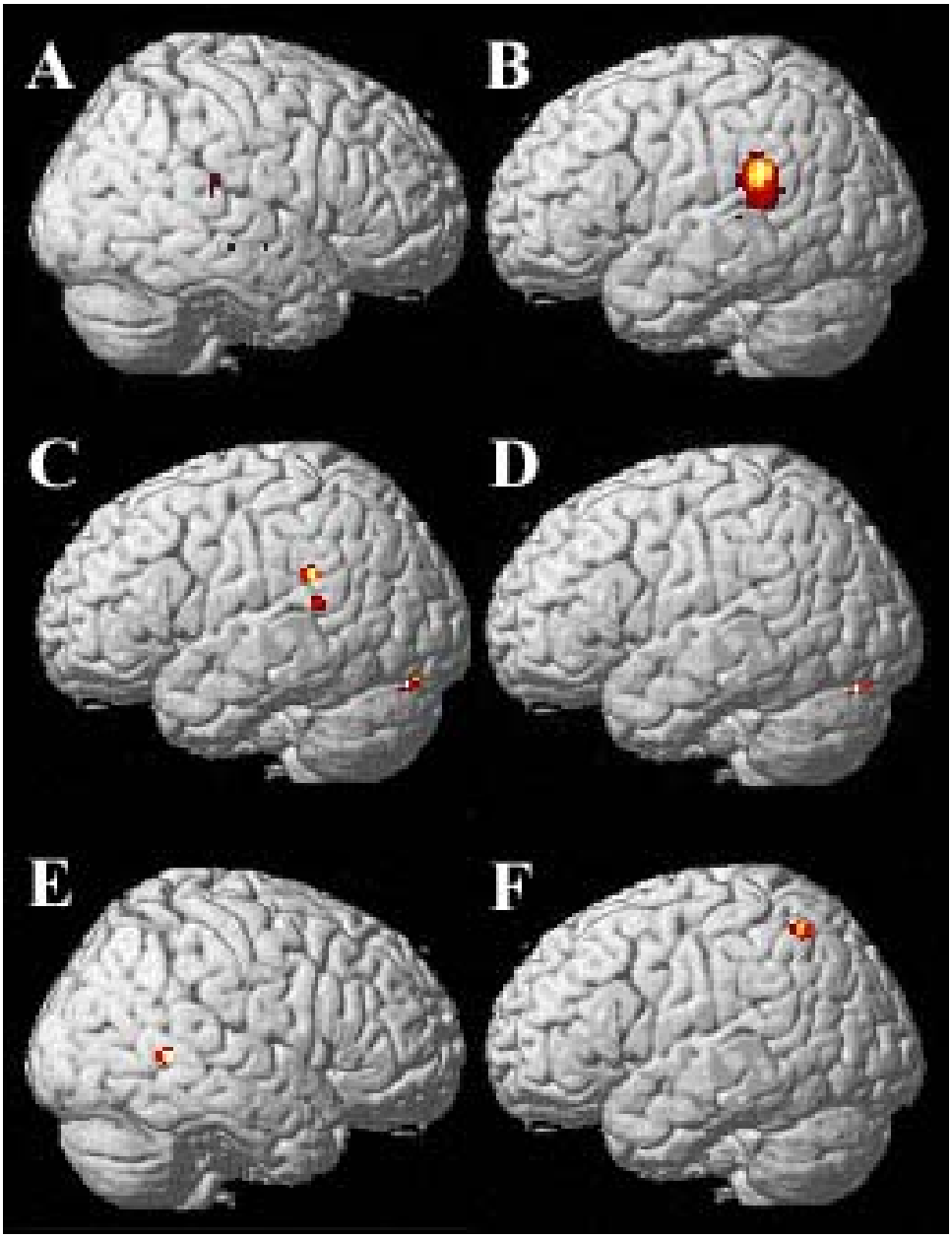

Figure 14: Correlating performance and brain activity changes showed significant positive correlations in the supramarginal gyrus (mainly on the left) and the left dorsolateral cerebellum ($p < 0.05$, corrected). A and B show the activation pattern for ITP 0-2, C for ITP 3-4, and D for ITP 5-6. E shows negative correlations for ITP 0-2 and F shows negative correlations for ITP 5-6. No significant negative correlations were seen for ITP 3-4.

Study B:

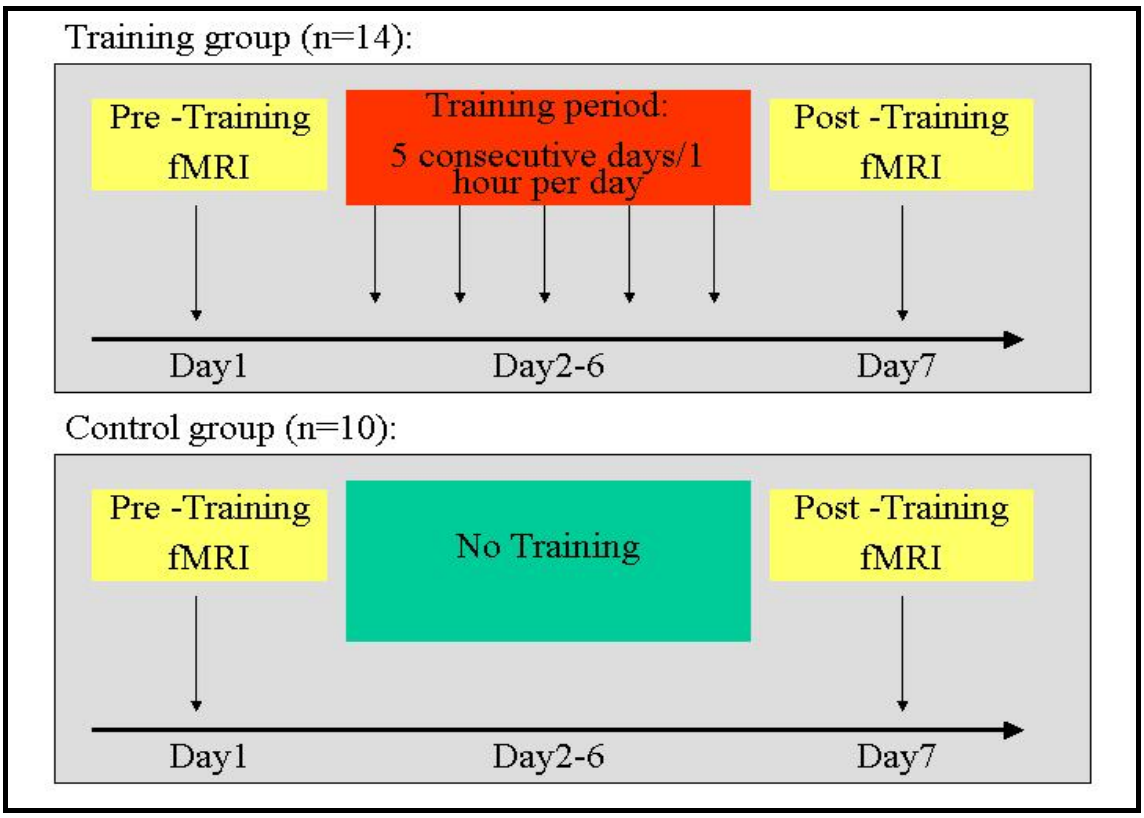

Figure 15: Experimental design

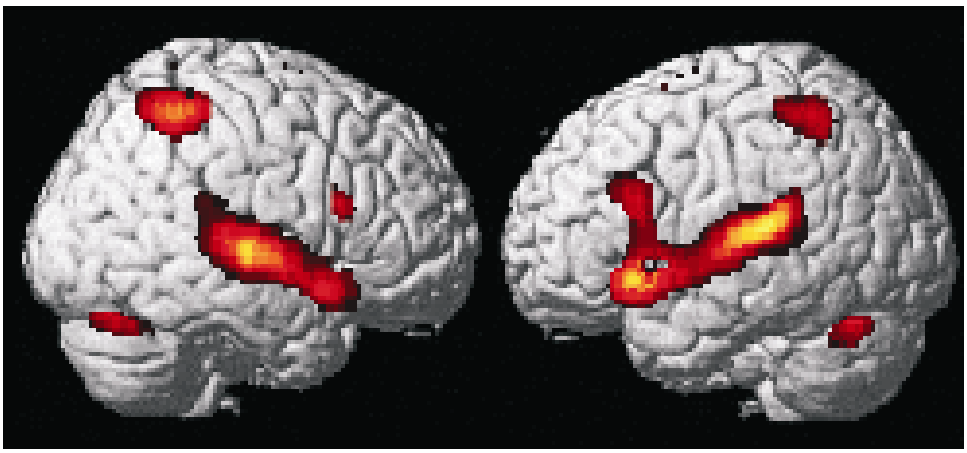

Figure 16: Pre-training mean image for entire training group (FWE-corrected)

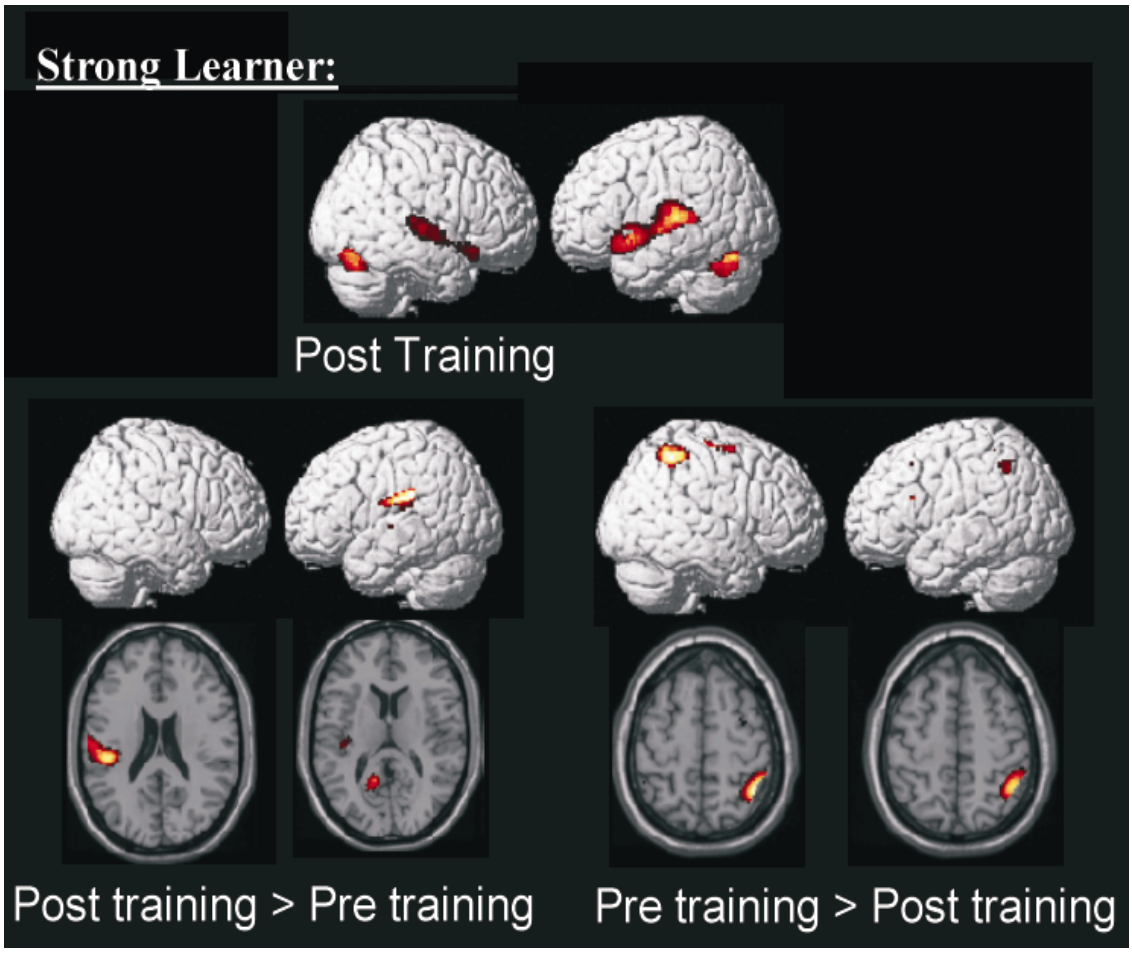

Figure 17: Brain activation pattern for the "strong" learner group (FWE-corrected).

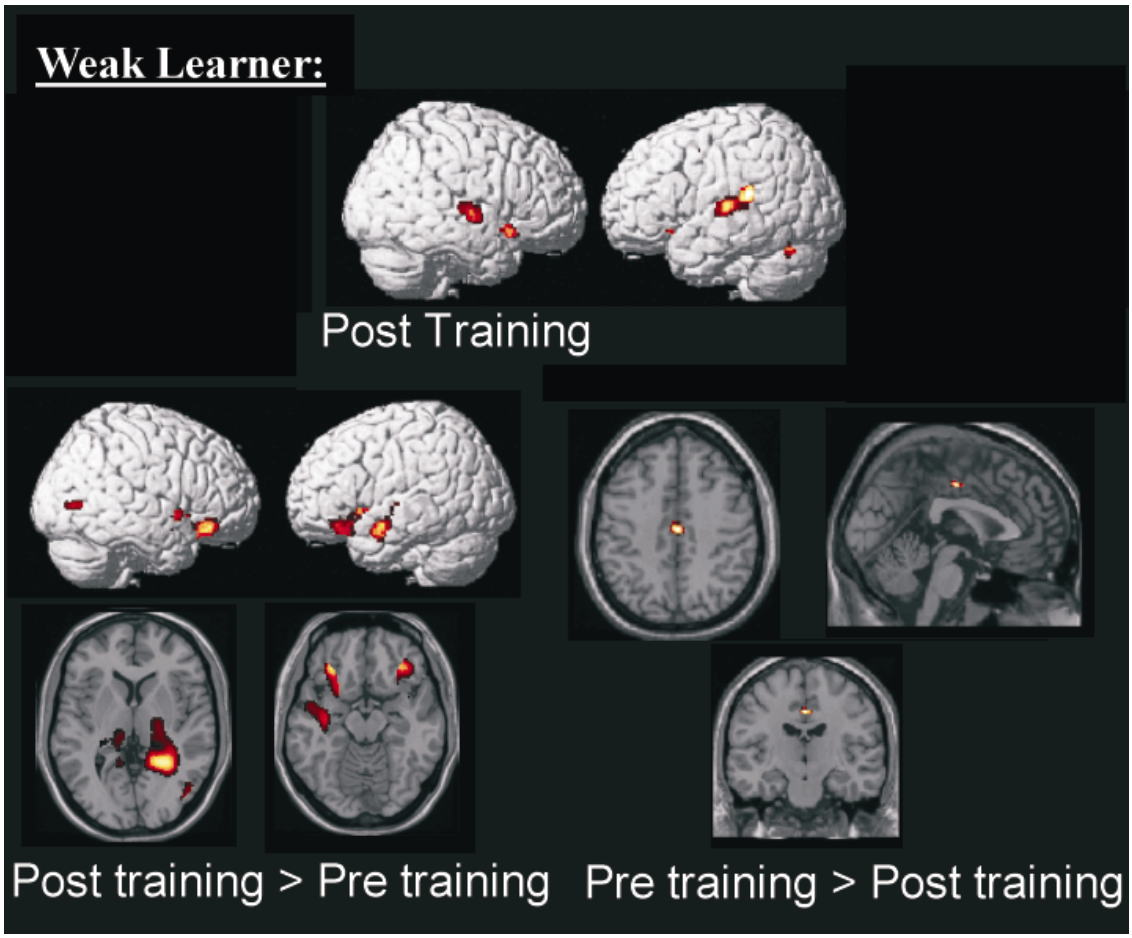

Figure 18: Brain activation pattern for the "weak" learner group (FWE-corrected)

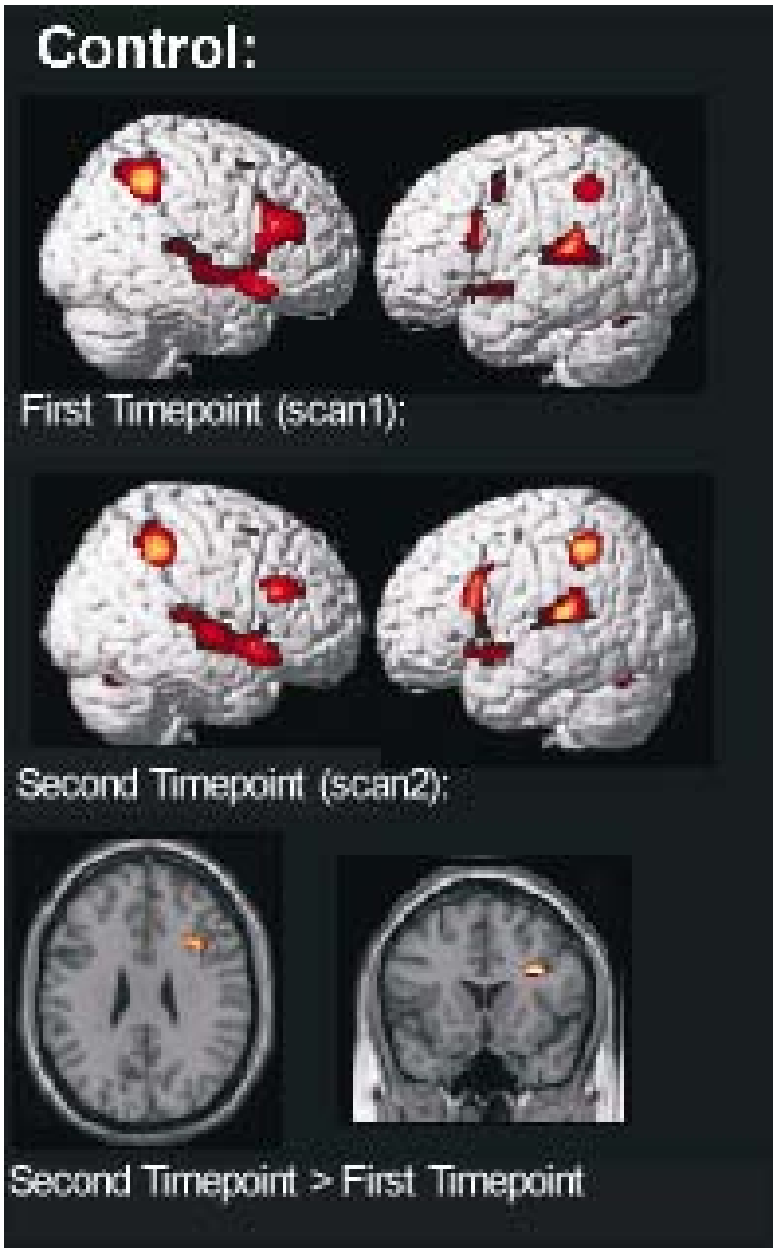

Figure 19: Brain activation for the control group (FWE-corrected).

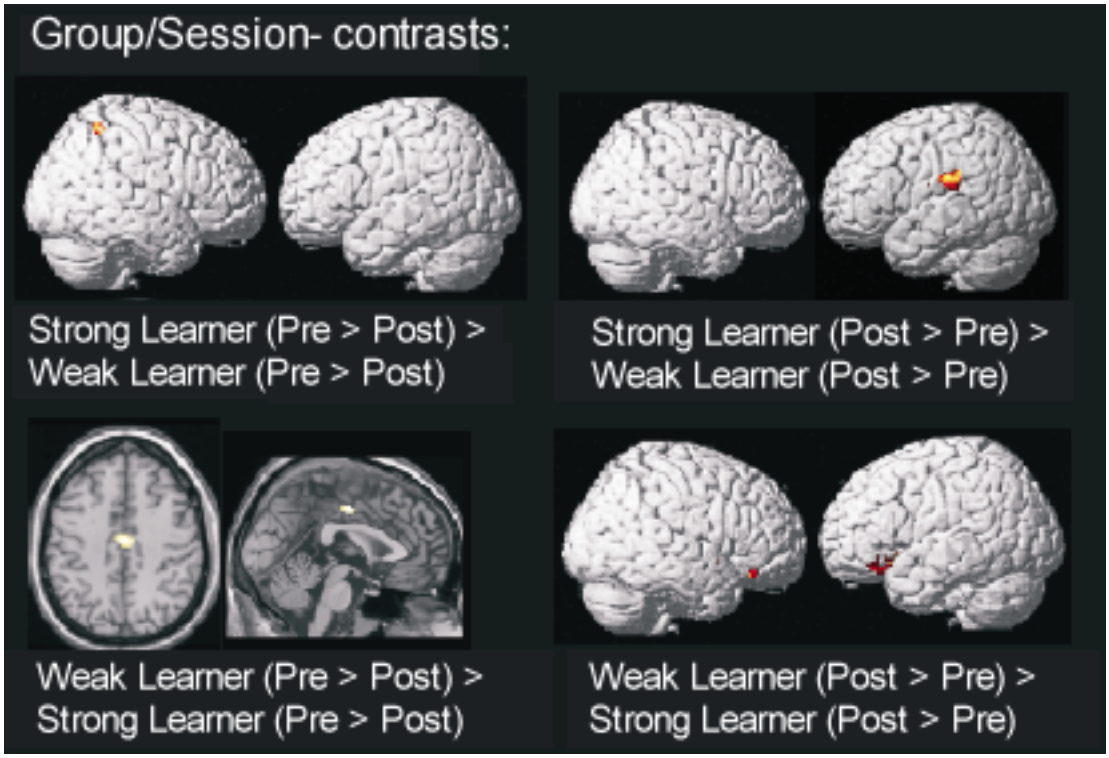

Figure 20: Pre-training versus post-training contrasts in "strong" versus "weak" learners (FWE-corrected).

Study C:

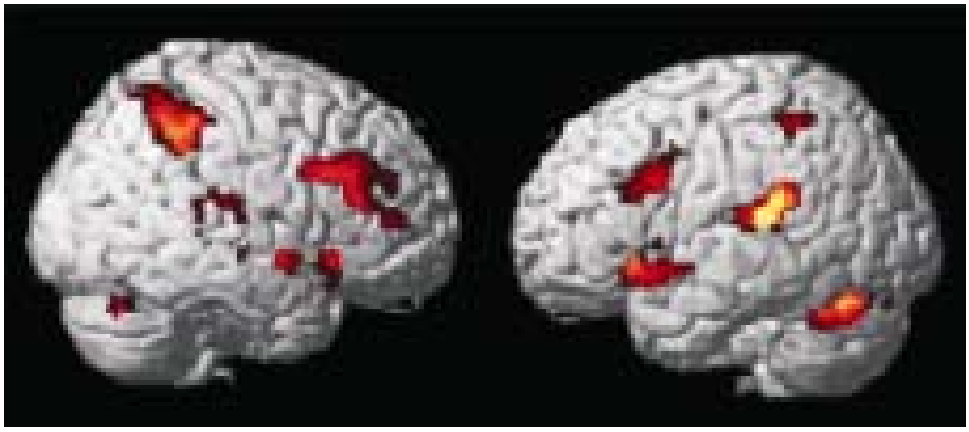

Figure 21: Mean images for musicians (Pitch Memory > motor control) for Imaging Time Point (ITP) 0-6 (p> 0.05, FDR-corrected)

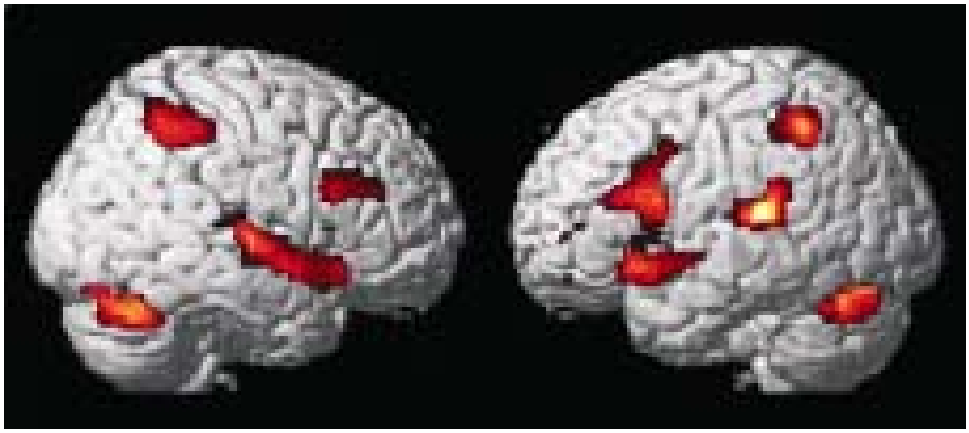

Figure 22: Mean images for non-musicians (Pitch Memory> Motor control) for ITP 0-6 (p < 0.05, FDR-corrected).

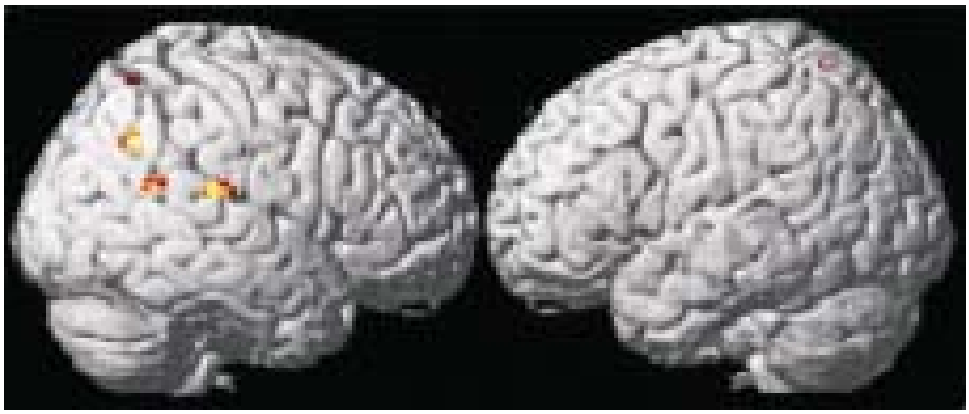

Figure 23: Contrast for musicians > non-musicians for ITP 0-3 ($p < 0.05$, FDR-corrected)

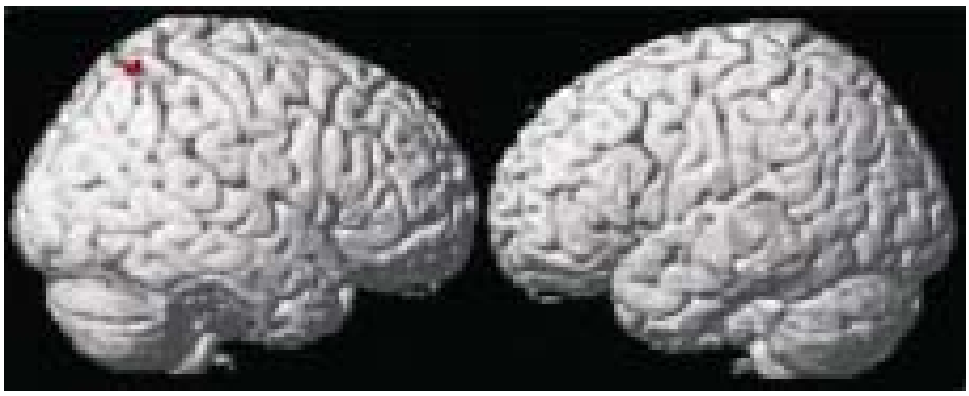

Figure 24: Contrast for musicians> non-musicians for ITP 4-6 ($p < 0.05$, FDR-corrected)

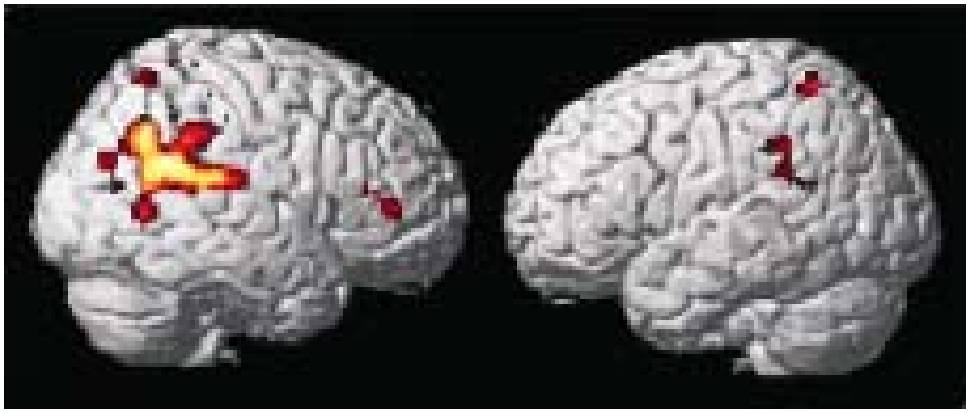

Figure 25: Contrast for musicians > non-musicians for ITP 0-3 ($p < 0.01$, uncorrected)

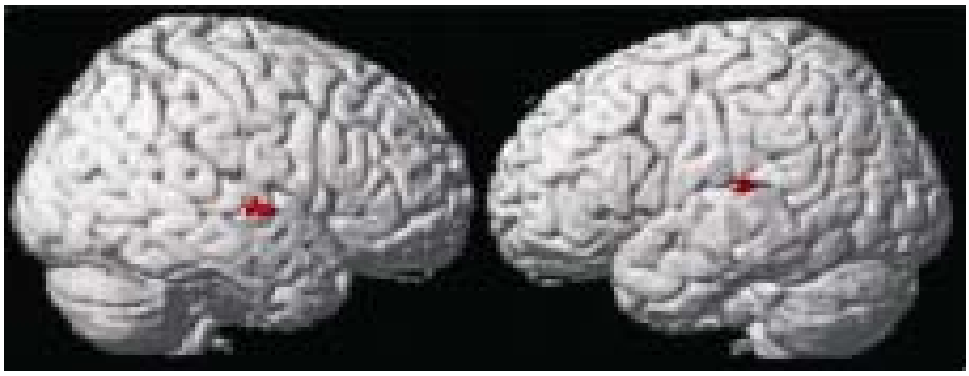

Figure 26: Contrast for non-musicians> musicians for ITP 0-3 ($p < 0.05$, FDR –corrected)

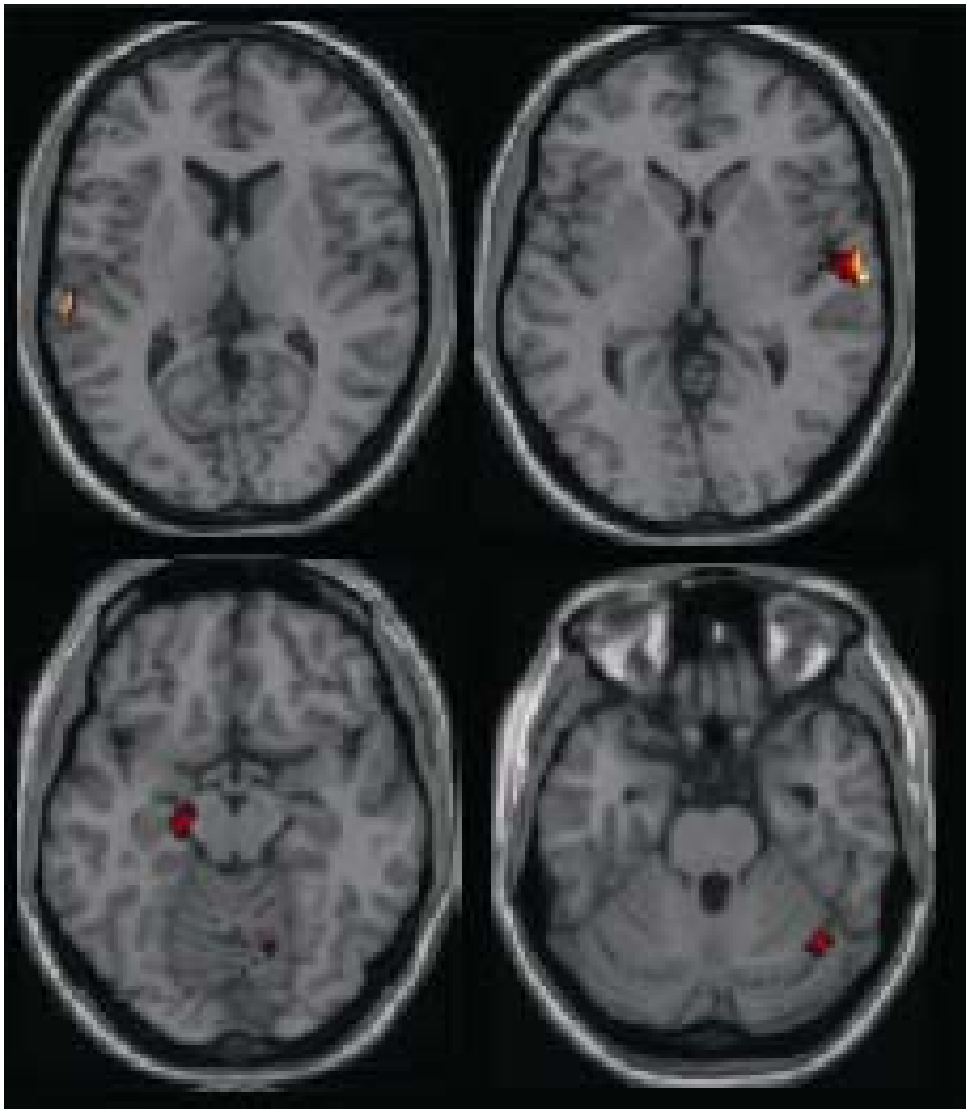

Figure 27: Contrast for non-musicians > musicians for ITP 0-3 ($p < 0.001$, uncorrected)

Study D:

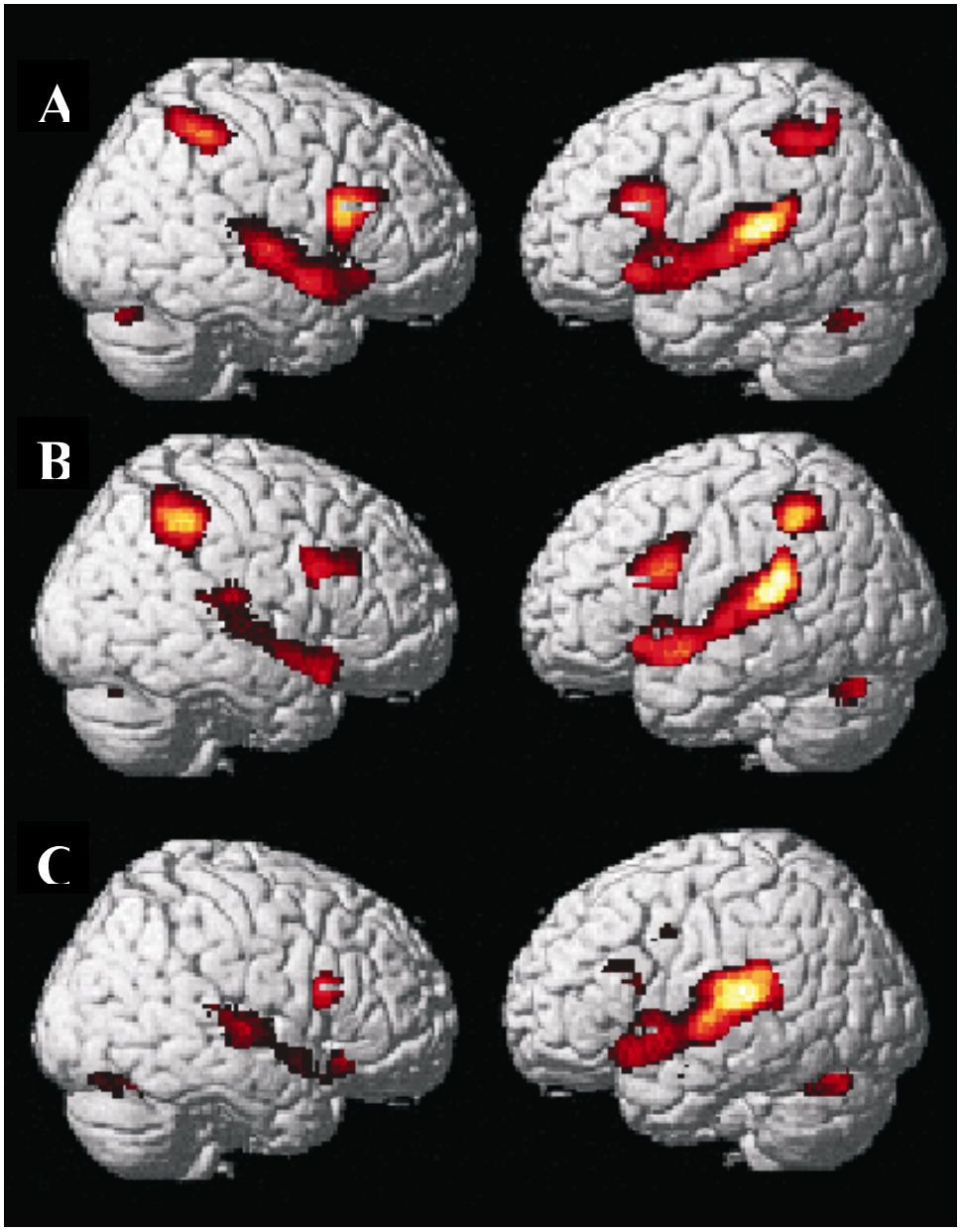

Figure 28: Mean images for (A) non-musicians prior to the training (B) musicians without training (C) non-musicians after the training (all FWE-corrected).

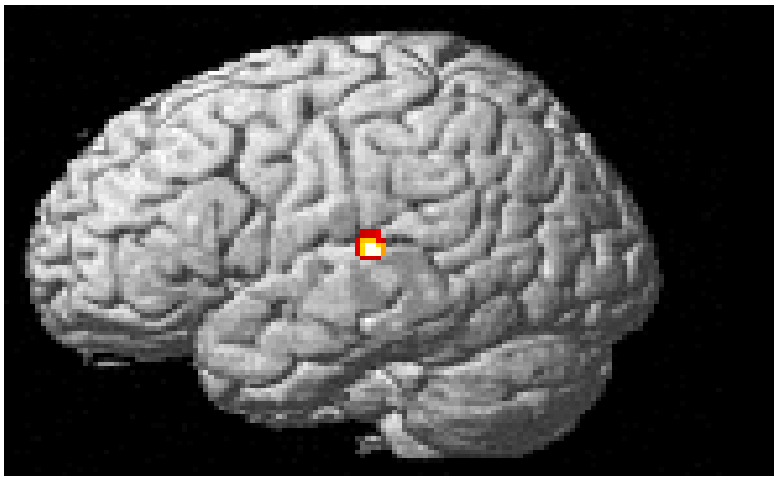

Figure 29: Contrast for non-musicians (prior to the training) > musicians (FDR-corrected).

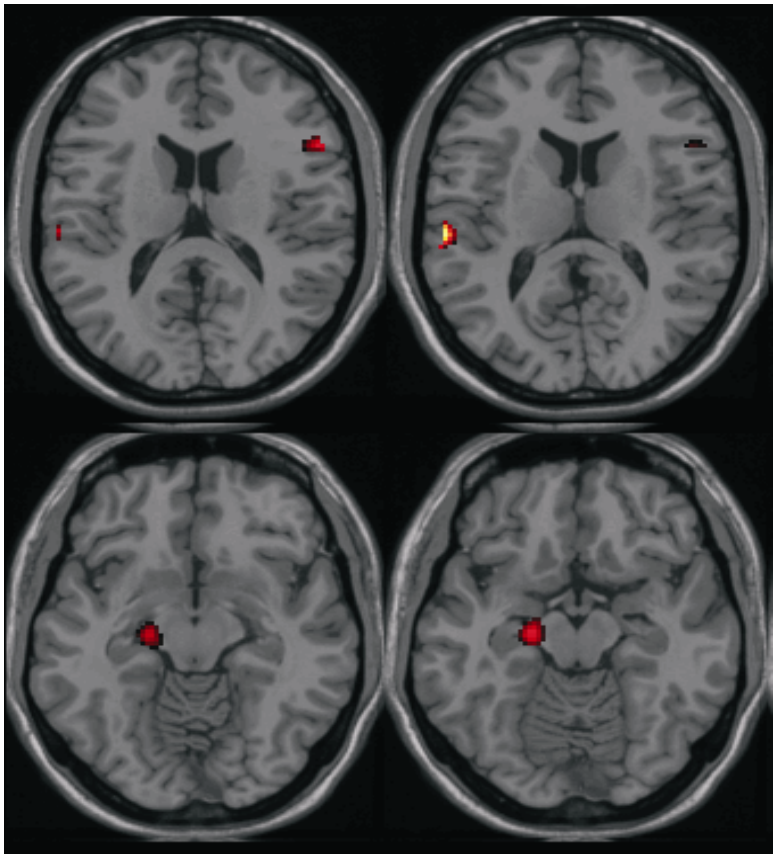

Figure 30: Contrast for non-musicians (prior to the training) > musicians (uncorrected: $p < 0.001$).

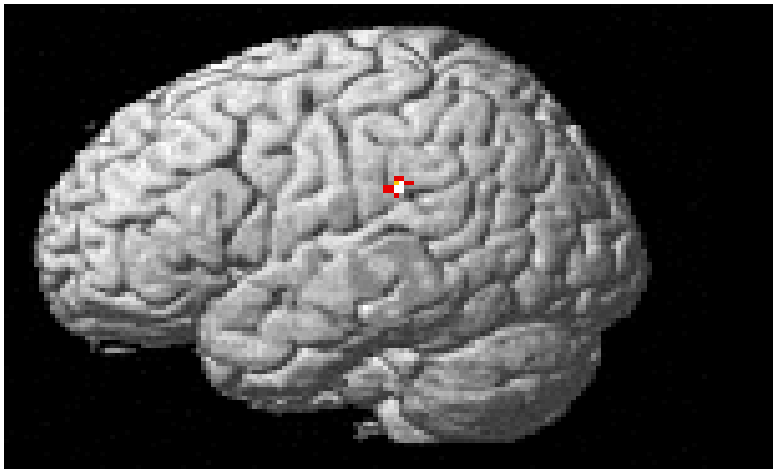

Figure 31: Contrast for musicians > non-musicians (prior to the training); (FDR-corrected, render view).

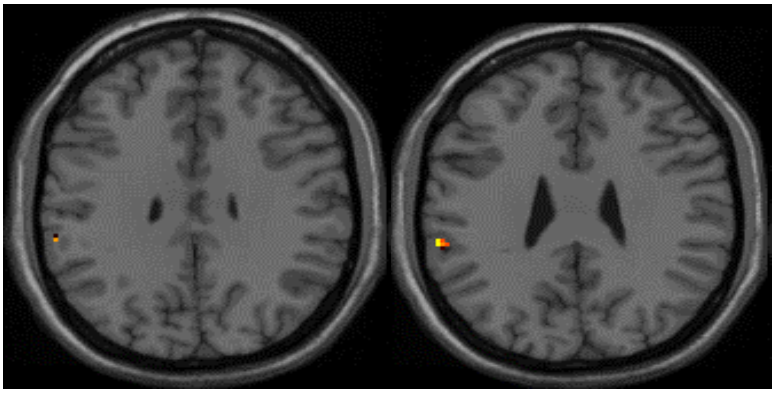

Figure 32: Contrast for musicians > non-musicians (prior to the training); (FDR corrected, axial slices).

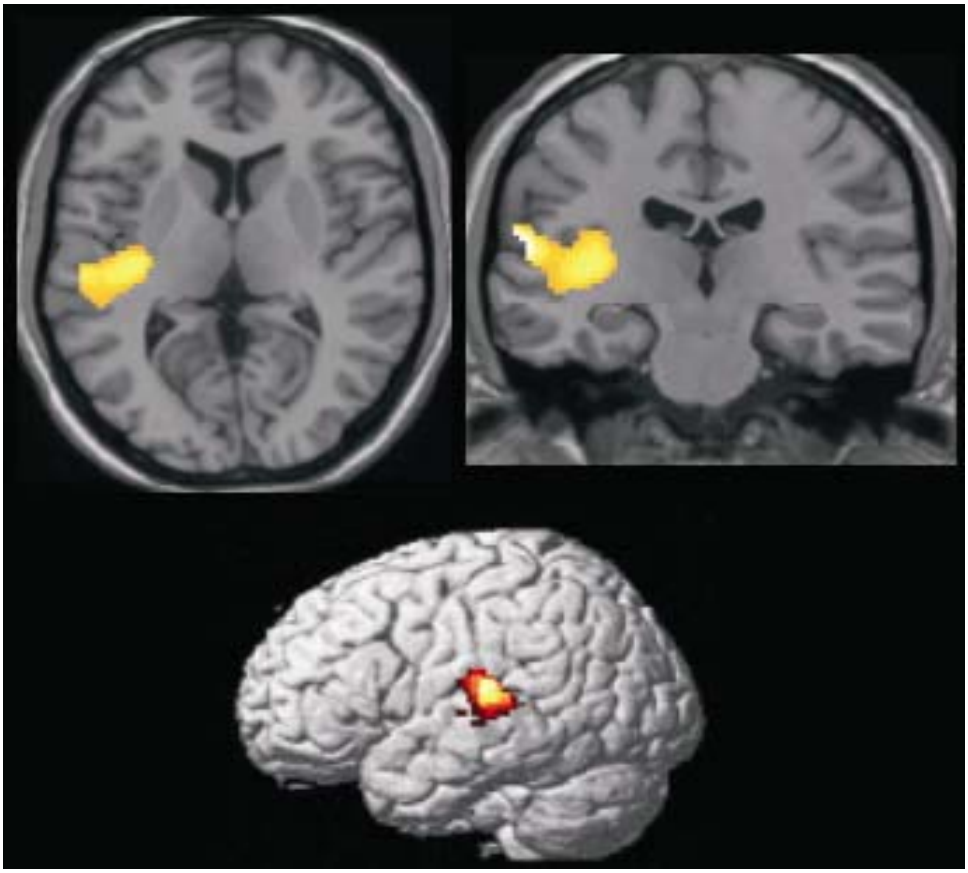

Figure 33: Contrast for non-musicians (after the training) > musicians; (FDR-corrected).

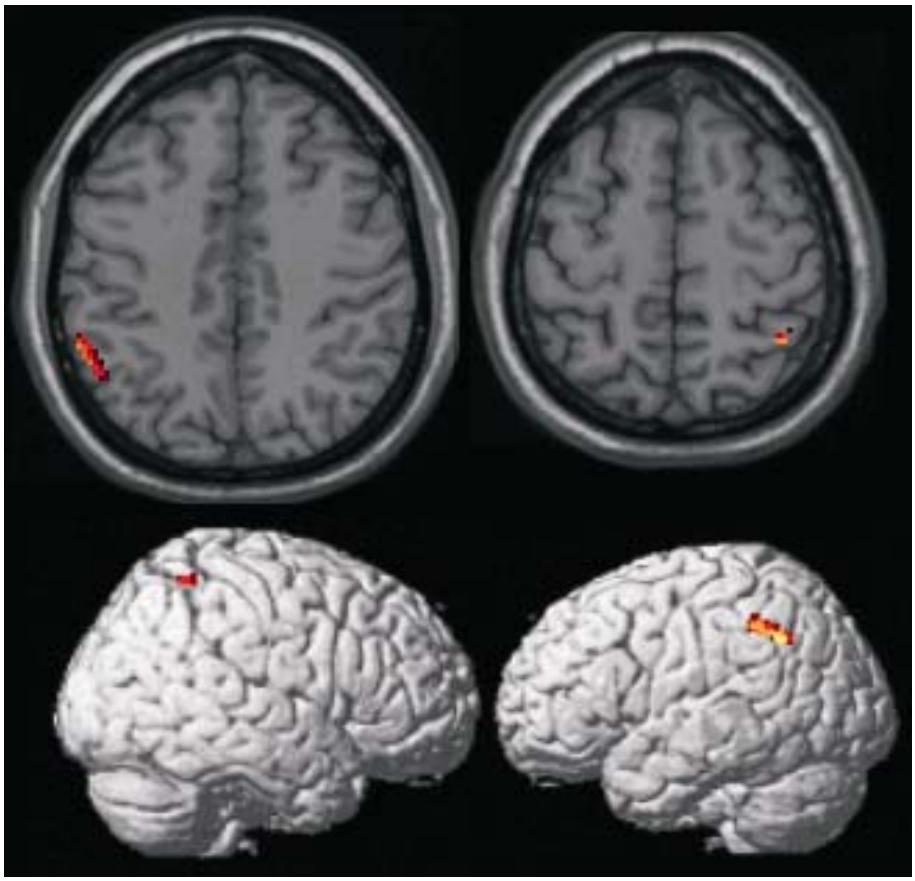

Figure 34: Contrast for musicians > non-musicians (after the training); (uncorrected: $p < 0.001$).

Study E:

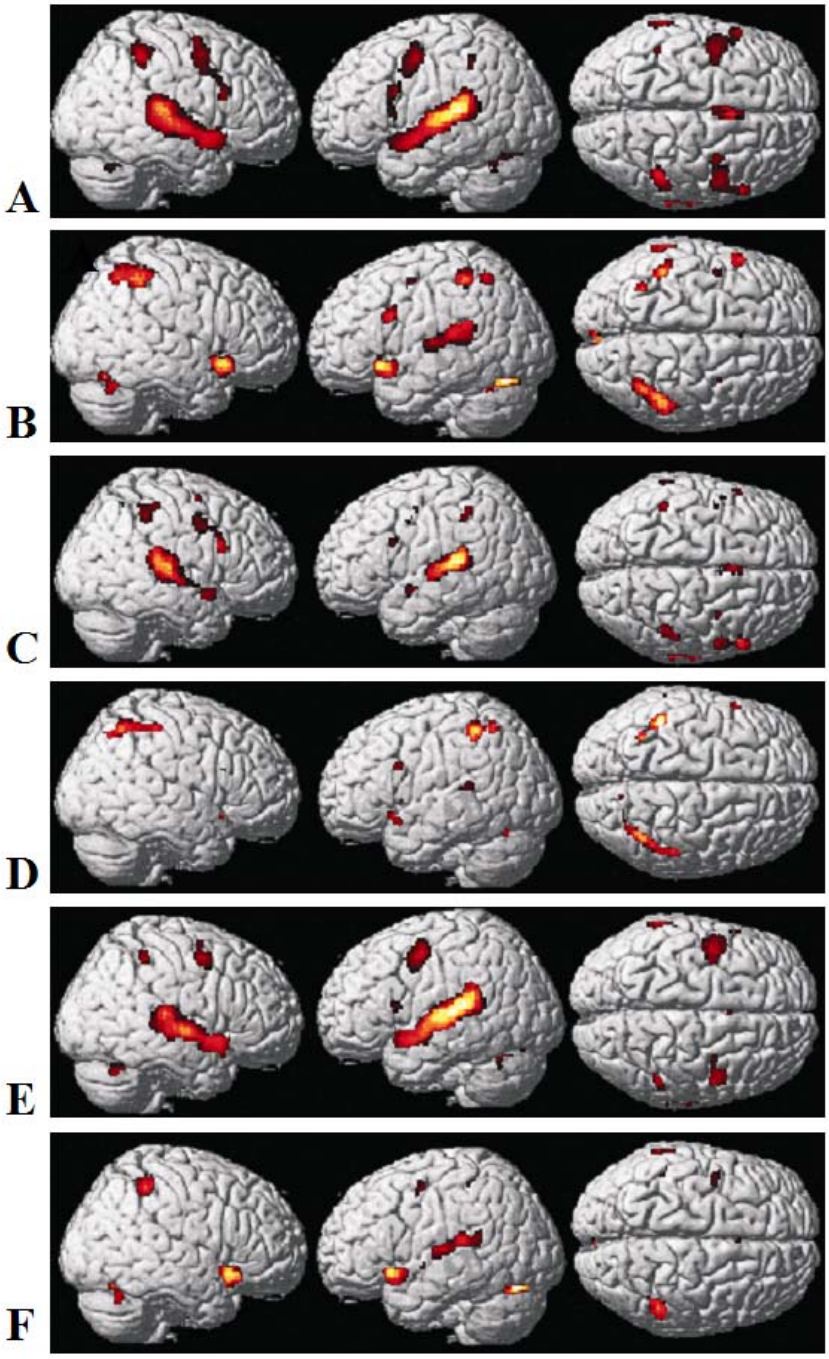

Figure 35: Group mean activation maps for the entire group as well as for the male and female subgroups. Fig. 35A (imaging time points 0-3s) and Fig. 35B (imaging time points 4-6s) show the entire group; Fig.35C (imaging time points 0-3s) and Fig. 35D (imaging time points 4-6s) show the female subgroup; Fig. 35E and Fig. 35F show the male subgroup.

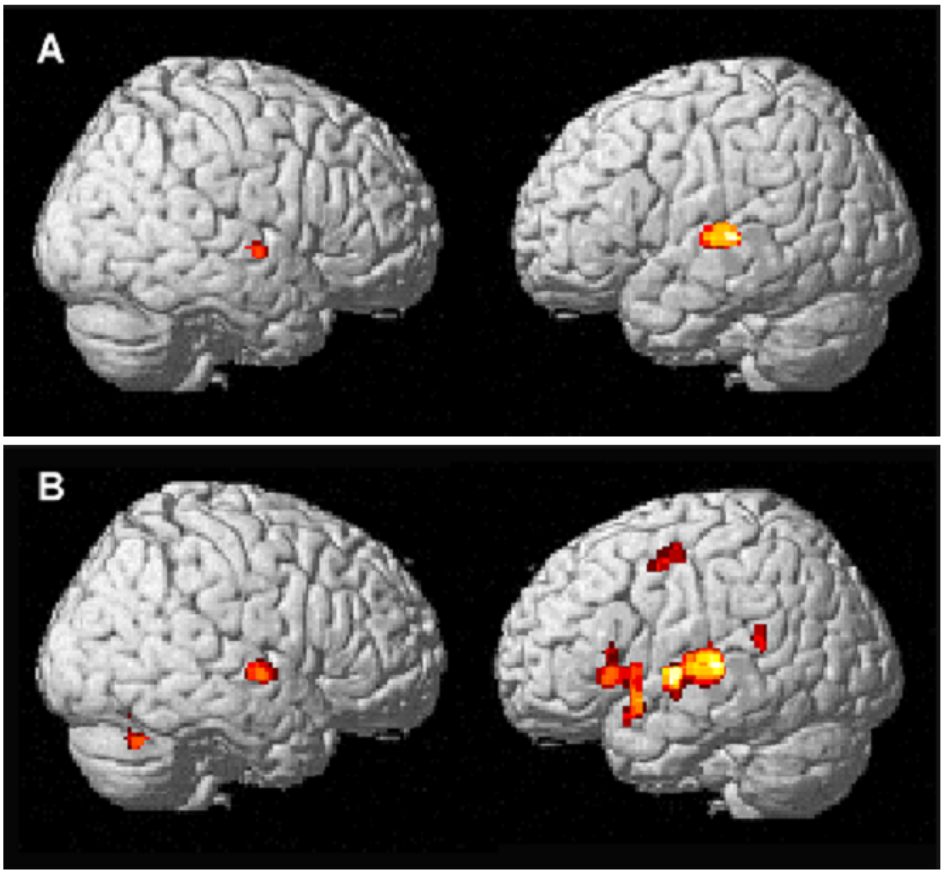

Figure 36: A) Significantly activated brain regions for the contrast "Males>Females" are presented for the early "perceptual" phase of the pitch memory task ($p < 0.05$, corrected for multiple comparisons (t values > 4.5)). No significant difference was seen for the contrast "Females>Males" in these early imaging time points. **B)** Additionally activated brain regions for the contrast "Males>Females" during the "perceptual" imaging time points using an uncorrected threshold ($P<.001$; significant after small volume correction; t-values >3.10). There was activation of the left frontal operculum (-48, 16.1, 0.4) in addition to a more extended activation of the superior temporal gyrus and posterior perisylvian region (-57.1, -47.9, 11.2). During the "perceptual" as well as during the "memory" phase, there was additional activation of the right cerebellum (20.3, -57.6, -22.6).

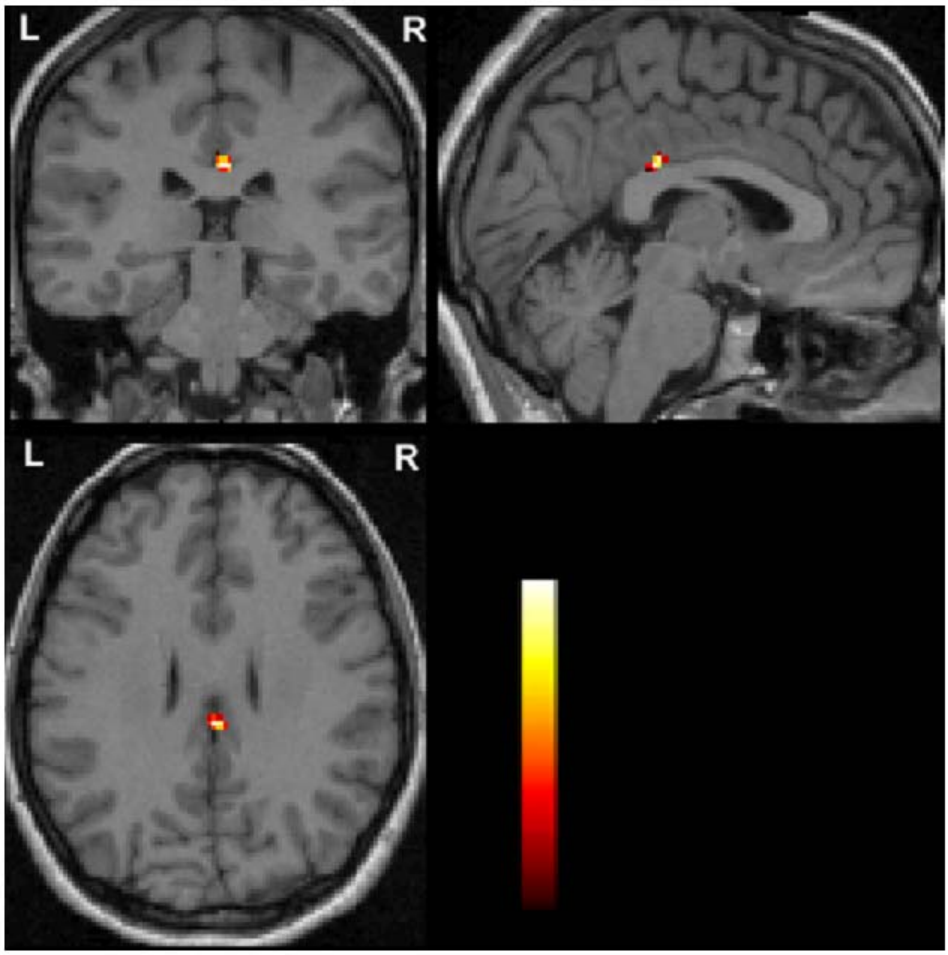

Figure 37: The contrast "Females>Males" showed no significant activations for the first imaging time points ("perceptual" phase), but a significant difference during the later imaging time points ("memory" phase) in the posterior-cingulate/retrosplenial region (1, -34.4, 20.7). Activations are significant at $p < 0.05$, corrected for multiple comparisons (t values > 4.5).

Study F:

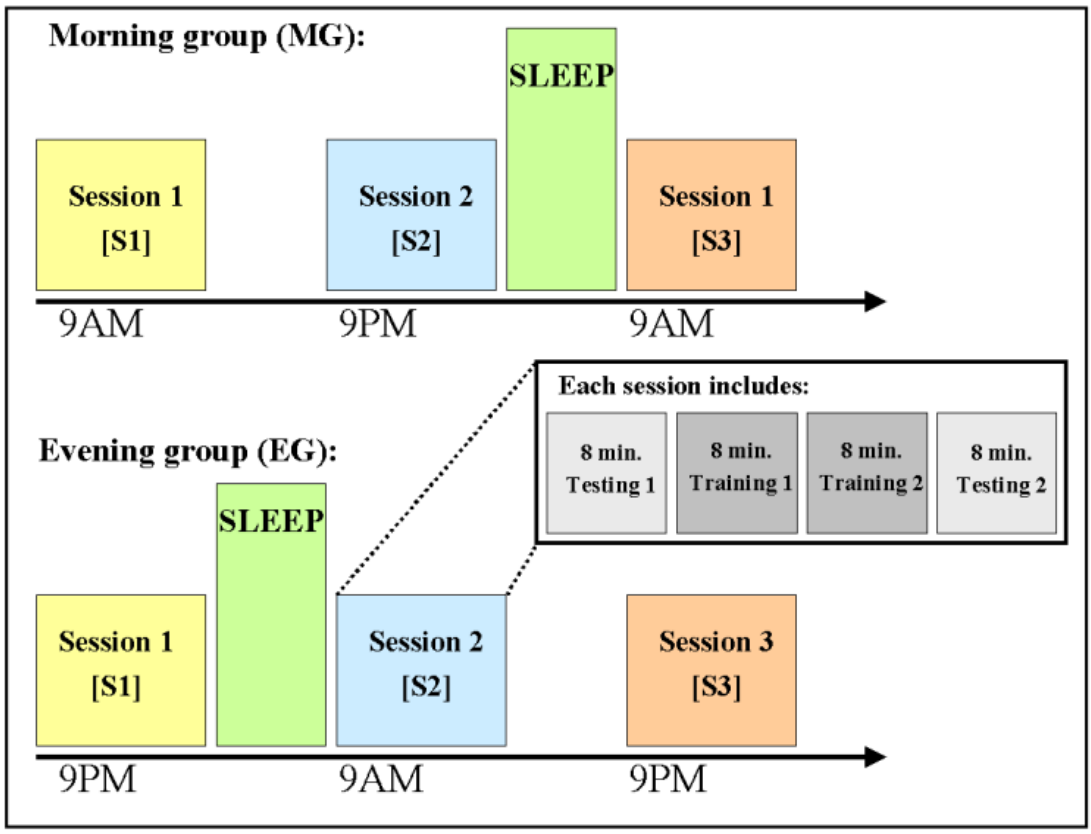

Figure 38: Experimental paradigm for Study F

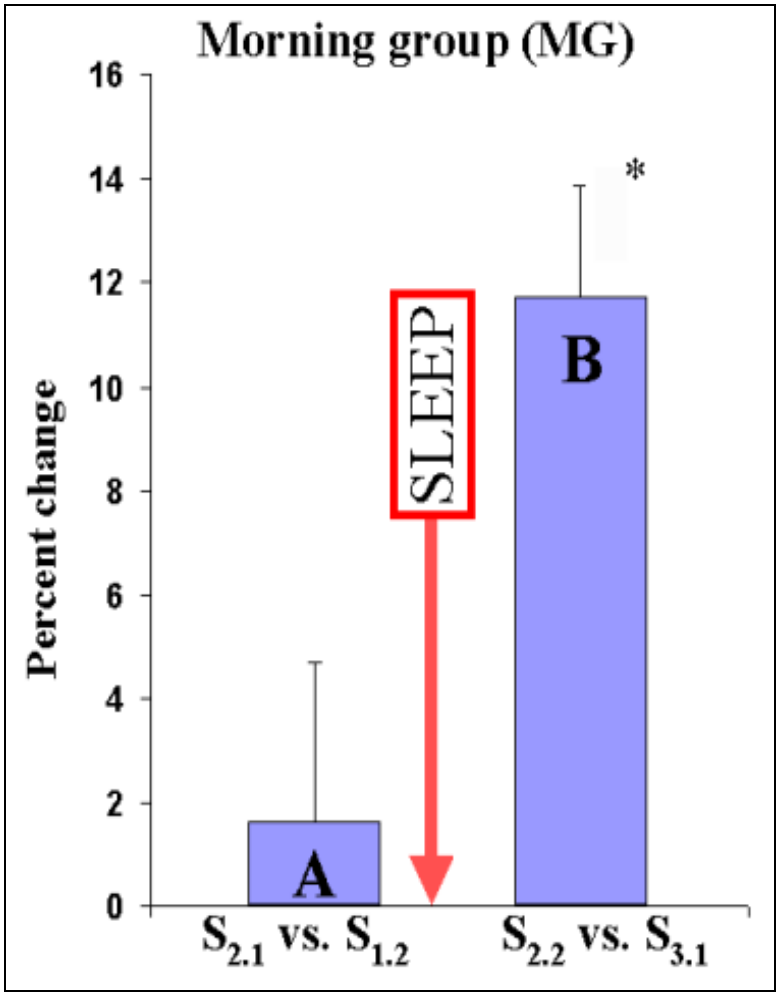

Figure 39: Percent change in performance rate for the morning group comparing (A) first testing in Session 2 [S2.1] with the second testing in Session 1 [S1.2] and (B) the first testing in Session 3 [S3.1] with the second testing in Session 2 [S2.2].

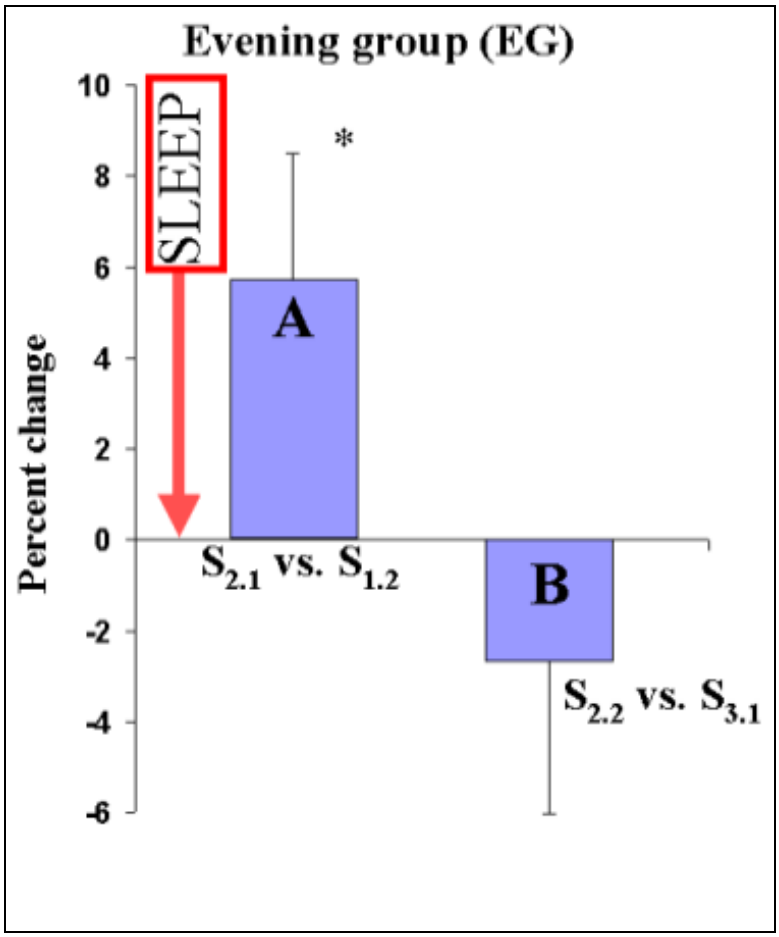

Figure 40: Percent change in performance rate for the evening group comparing (A) first testing in Session 2 [S2.1] with the second testing in Session 1 [S1.2] and (B) the first testing in Session 3 [S3.1] with the second testing in Session 2 [S2.2].

Own publications:

Paper in peer reviewed journals:

Gaab, N., Paetzold, M., Becker, M., Walker, M.P. & Schlaug, G. (2004). The influence of sleep on auditory learning-a behavioral study. *Neuroreport,* 15(4):731-734.

Gaab, N., Gaser, C., Zaehle, T., Jancke, L. & Schlaug, G. (2003). Functional anatomy of pitch memory- an fMRI study with sparse temporal sampling. *Neuroimage*, 19(4): 1417-1426.

Gaab, N., Keenan, J. & Schlaug, G. (2003). The effects of gender on the neural substrates of pitch memory. *J. Cogn. Neurosci.*, 15(6): 810-820.

Gaab, N. & Schlaug, N. (2003). The effect of musicianship on pitch memory in performance matched groups. *Neuroreport*, 14(18): 2291-2295.

Gaab, N. & Schlaug, G. (2003). Musicians differ from nonmusicians in brain activation despite performance matching. *Ann. N.Y. Acad. Sci.*, 999: 385-389.

Hutchinson, S., Lee, L.H., Gaab, N. & Schlaug, G. (2003). Cerebellar volume differences between musicians and non-musicians. *Cereb. Cortex*, 13: 943-949.

Jancke, L., Gaab, N., Wüstenberg, T., Scheich, H. & Heinze, H.J.(2001). Short-term functional plasticity in the human auditory cortex: an fMRI study. *Brain Res. Cogn. Brain Res.*, 12: 479-485.

Ihl, R., Grass-Kapanke, B., Lahrem, P., Brinkmeyer, J., Fischer, S., Gaab, N. & Kaupmannsennecke, C. (2000). Entwicklung und Validierung eines Tests zur Früherkennung der Demenz mit Depressionsabgrenzung (TFDD). *Fortschr. Neurol. Psychiat.*, 68: 413-422.

Unreviewed papers:

Jancke, L., Gaab, N., Wüstenberg, T., Scheich, H. & Heinze, H.J. (2001). Short-term functional plasticity in the human auditory cortex: an fMRI study. *Magdeburger Arbeiten zur Psychologie*, 3(1): 1-13.

Book chapters:

Schlaug, G. & Gaab, N. (2003). Das musizierende Gehirn: Strukturelle und funktionelle Unterschiede zwischen Musikern und Nicht-Musikern.In: Musik und Humanitaet; Interdisziplinaere Grundlagen fuer (musikalische) Erziehung und Bildung. Eds.: Bastian, H.G. and Kreutz, G.; Schott Musik International: 120-134.

Conference papers, abstracts, posters and oral presentations :

Gaab, N., Ozdemir, E., Overy, K. & Schlaug, G. (2004). Shared neural substrates for singing, speaking and humming. Poster presented at "Eleventh Annual Meeting of the Cognitive Neuroscience Society" in San Francisco, CA April 2004.

Gaab, N., Schulze, K., Ozdemir, E. & Schlaug, G. (2004). Extensive activation of occipital and parietal cortex in a blind absolute pitch musician. Poster presented at "Eleventh Annual Meeting of the Cognitive Neuroscience Society" in San Francisco, CA April 2004.

Gaab, N., Walker, M.P. & Schlaug, G. (2003). The influence of sleep on auditory learning- a behavioral study. Poster presented at: "Society for Neuroscience. 33rd Annual meeting" in New Orleans, LA November 2003.

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Gaab, N., Gaser, C., Chen, Y. & Schlaug, G. (2002). Exploring neural correlates of musical functions using a sparse temporal sampling fMRI method. Poster presented at: "Sixth international conference on cognitive and neural systems" in Boston, MA May 2002.

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